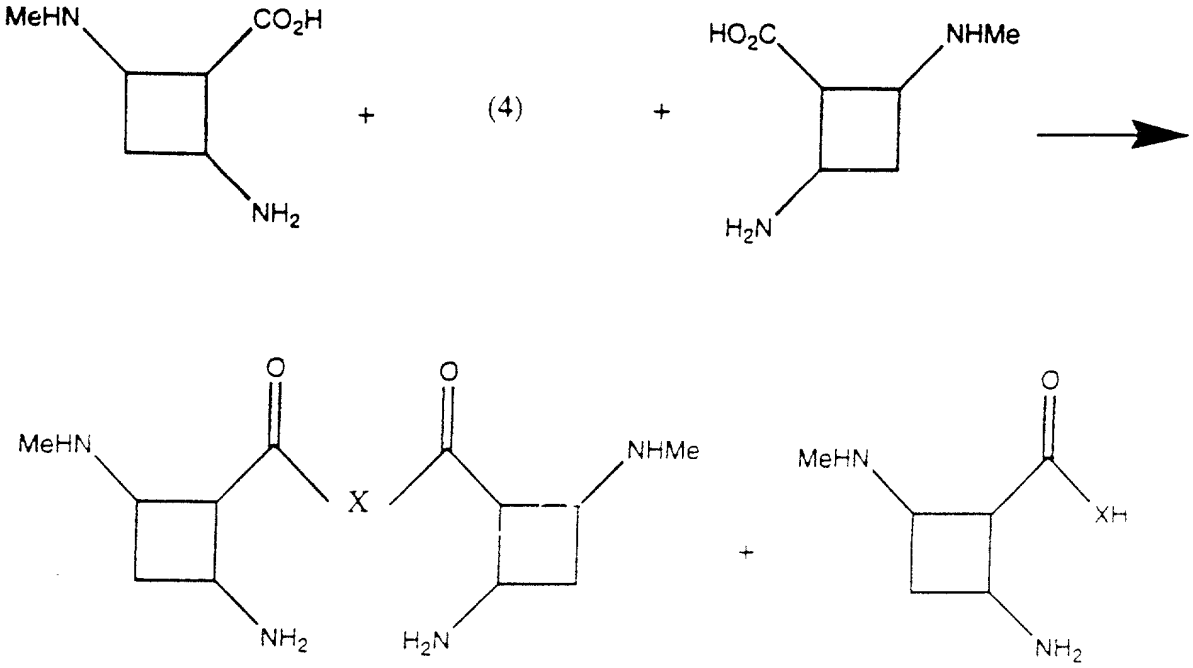
REACTION SCHEME 2

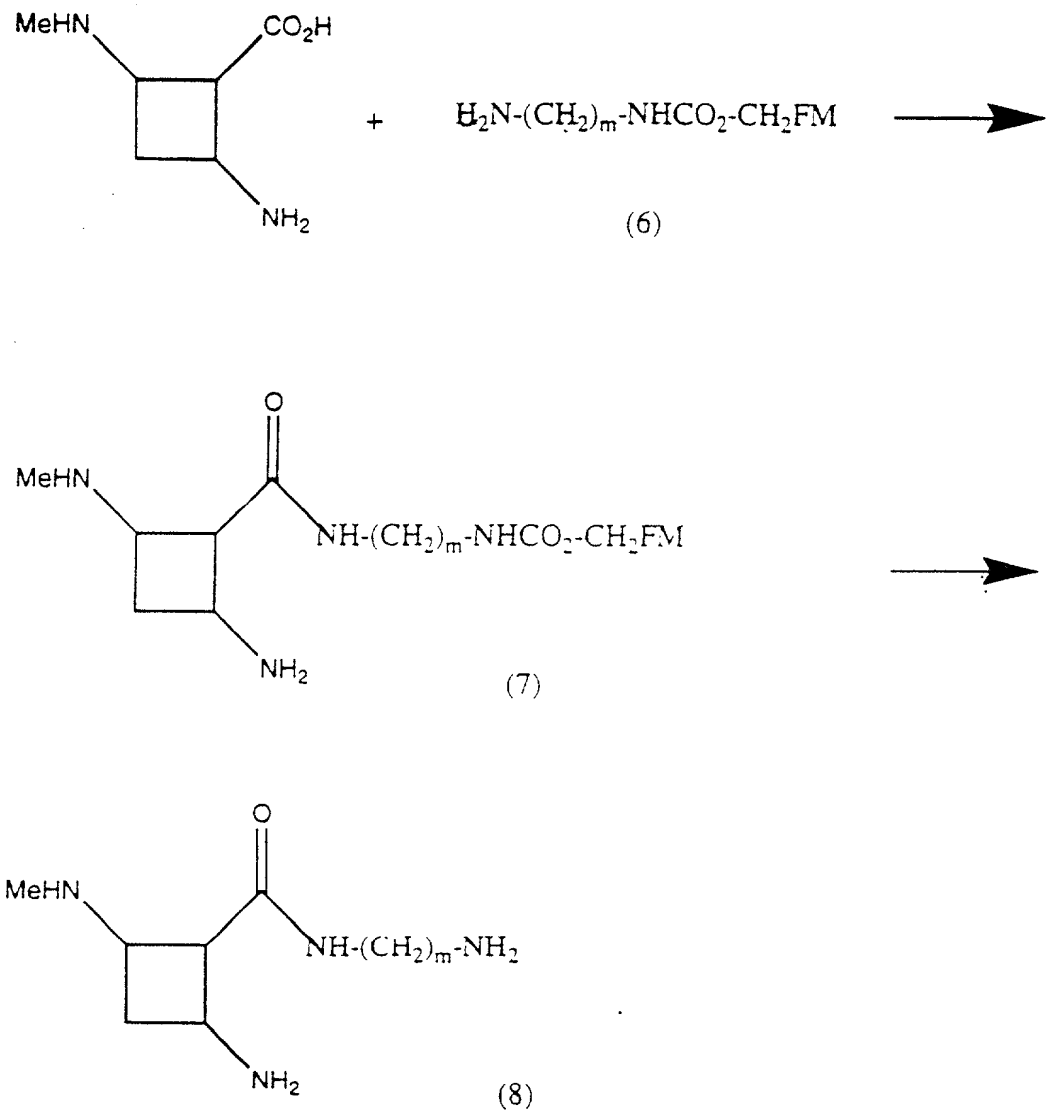


Formula 1

(5)

FIGURE 1

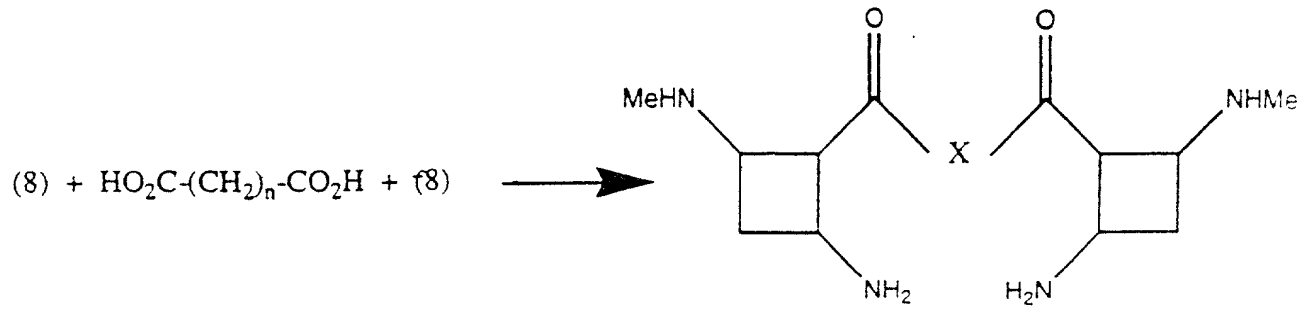
REACTION SCHEME 3



Where FM represents 9-fluorenyl., and m is an integer of 1-20

FIGURE 2

REACTION SCHEME 4



Formula I

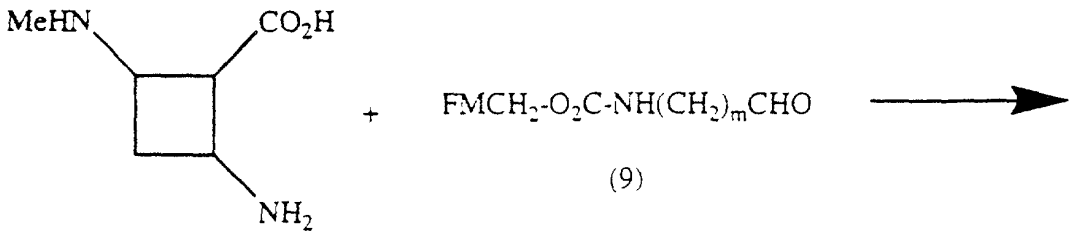
where X is a linker of formula:

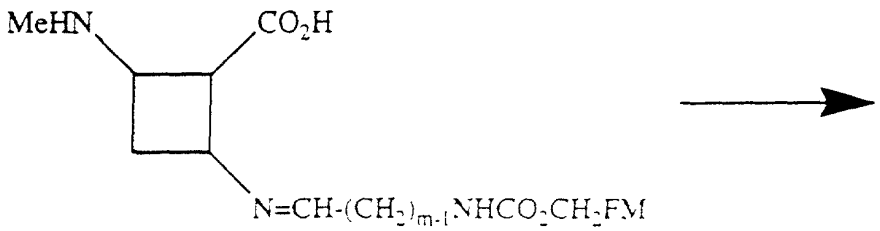
$$-NH-(CH_2)_mNHC(O)(CH_2)_nC(O)NH(CH_2)_m-NH-$$

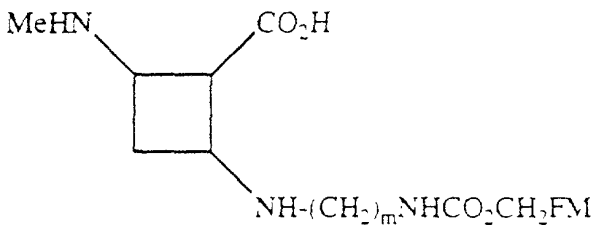
in which m and n are independently integers of 1-20.

FIGURE 3

REACTION SCHEME 5



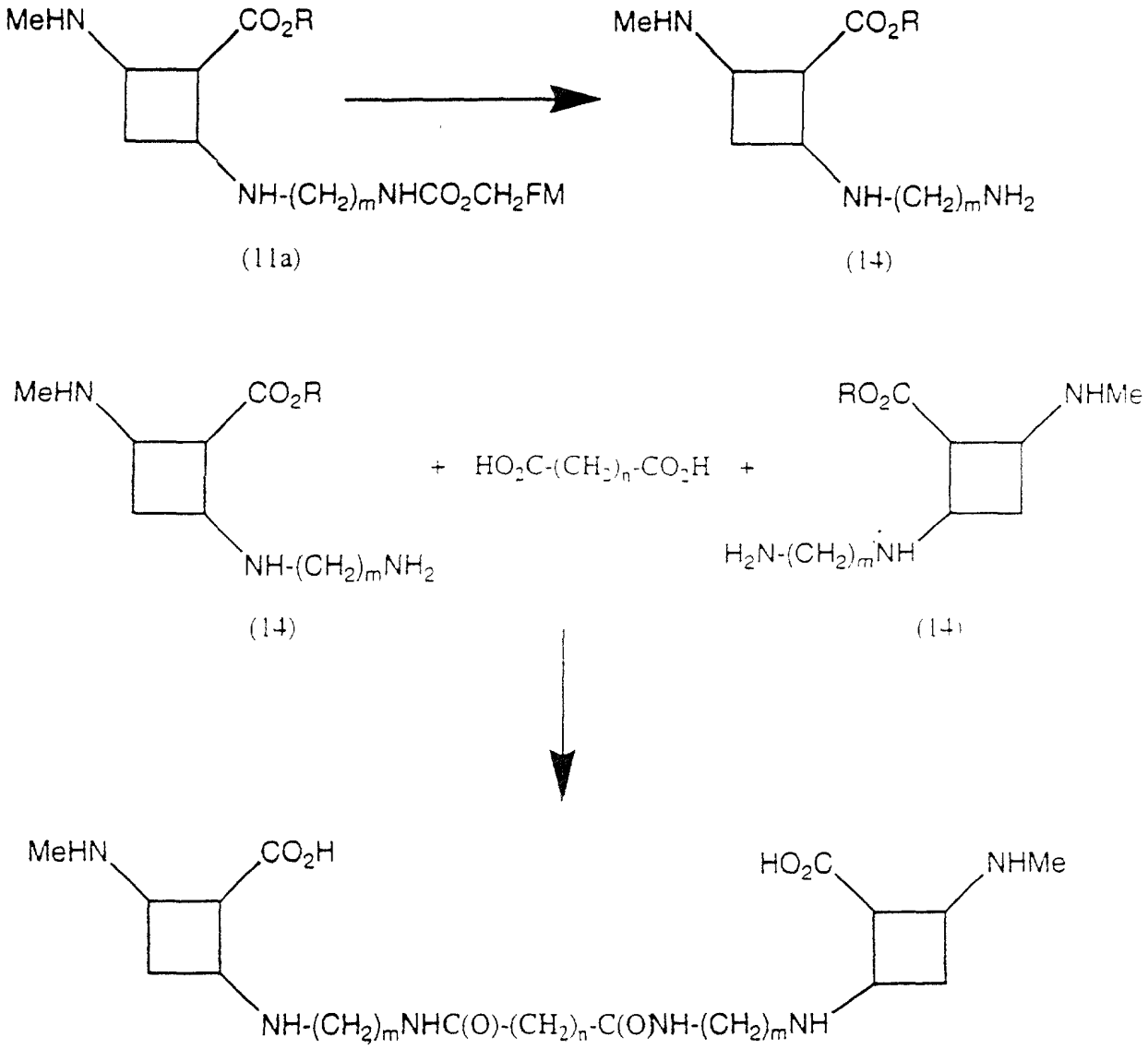




in which m is an integer of 1-20, and FM is 9-fluorenyl.

FIGURE 4

REACTION SCHEME 6

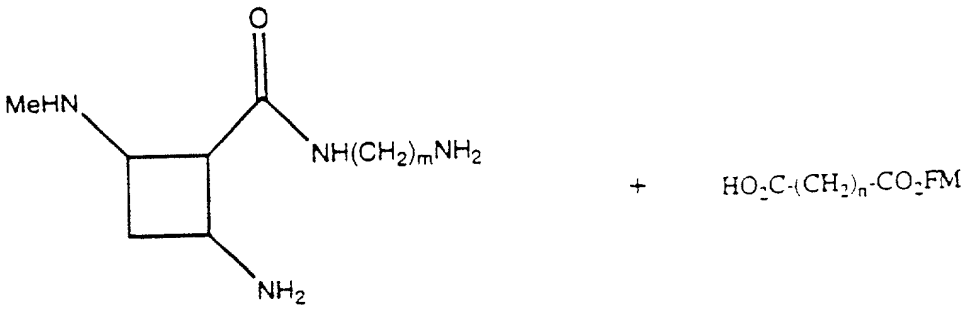


Formula I

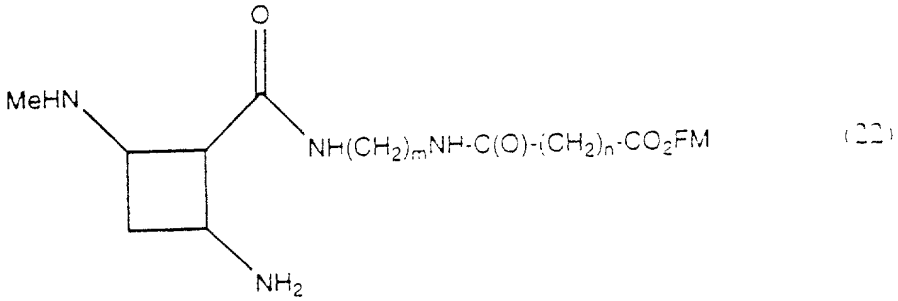
where R is a protecting group, such as an ester, m and n are as defined above, and FM is 9-fluorenyl

FIGURE 5

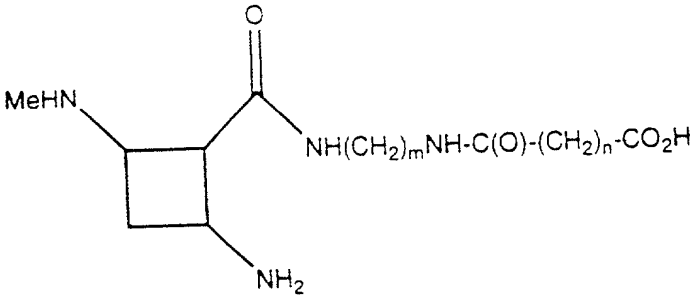
REACTION SCHEME 7



(8)



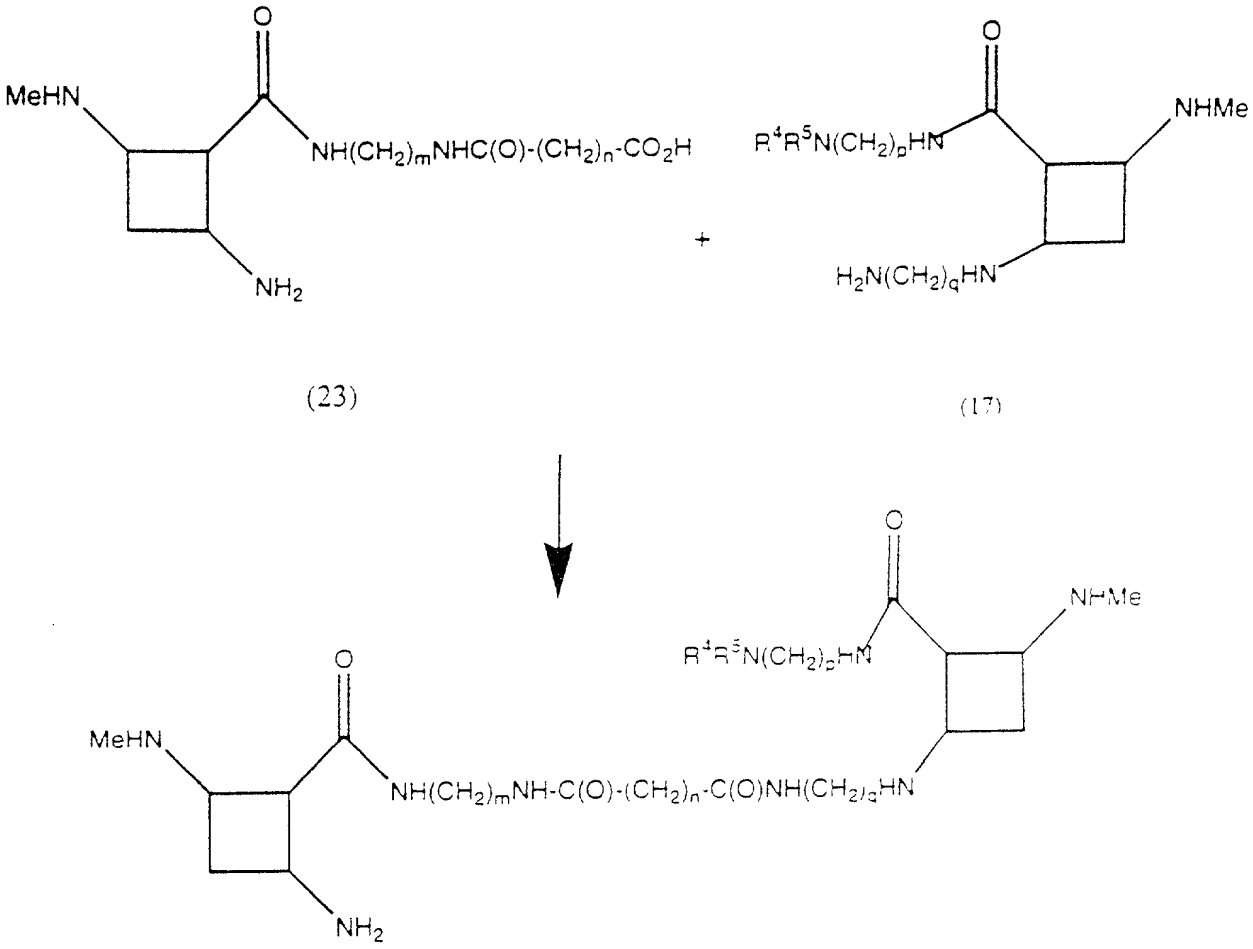
(22)



(23)

FIGURE 6

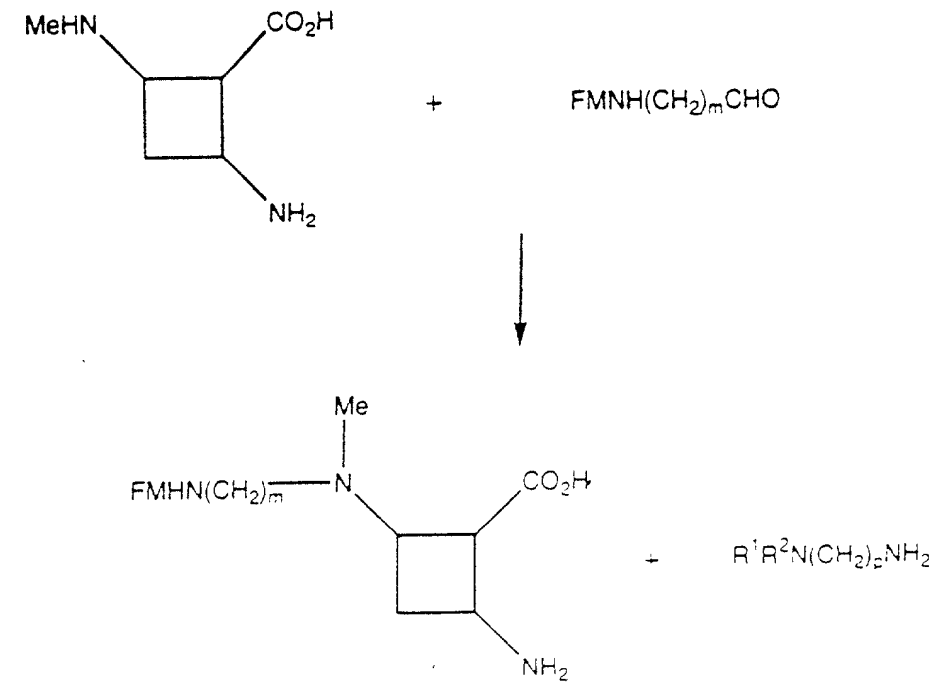
REACTION SCHEME 8



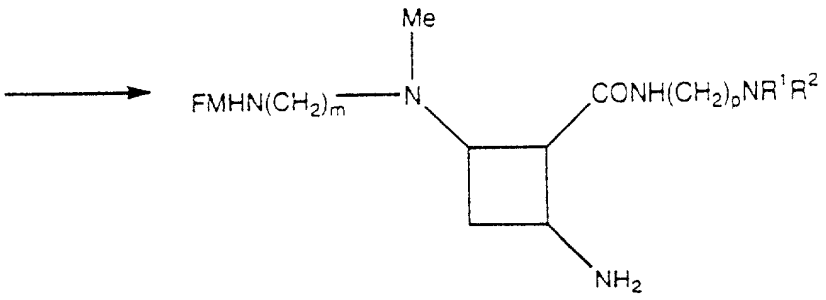
Formula I

FIGURE 7

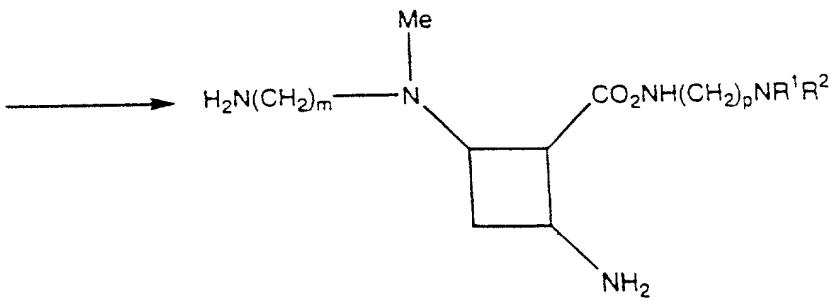
REACTION SCHEME 9



(24)



(25)

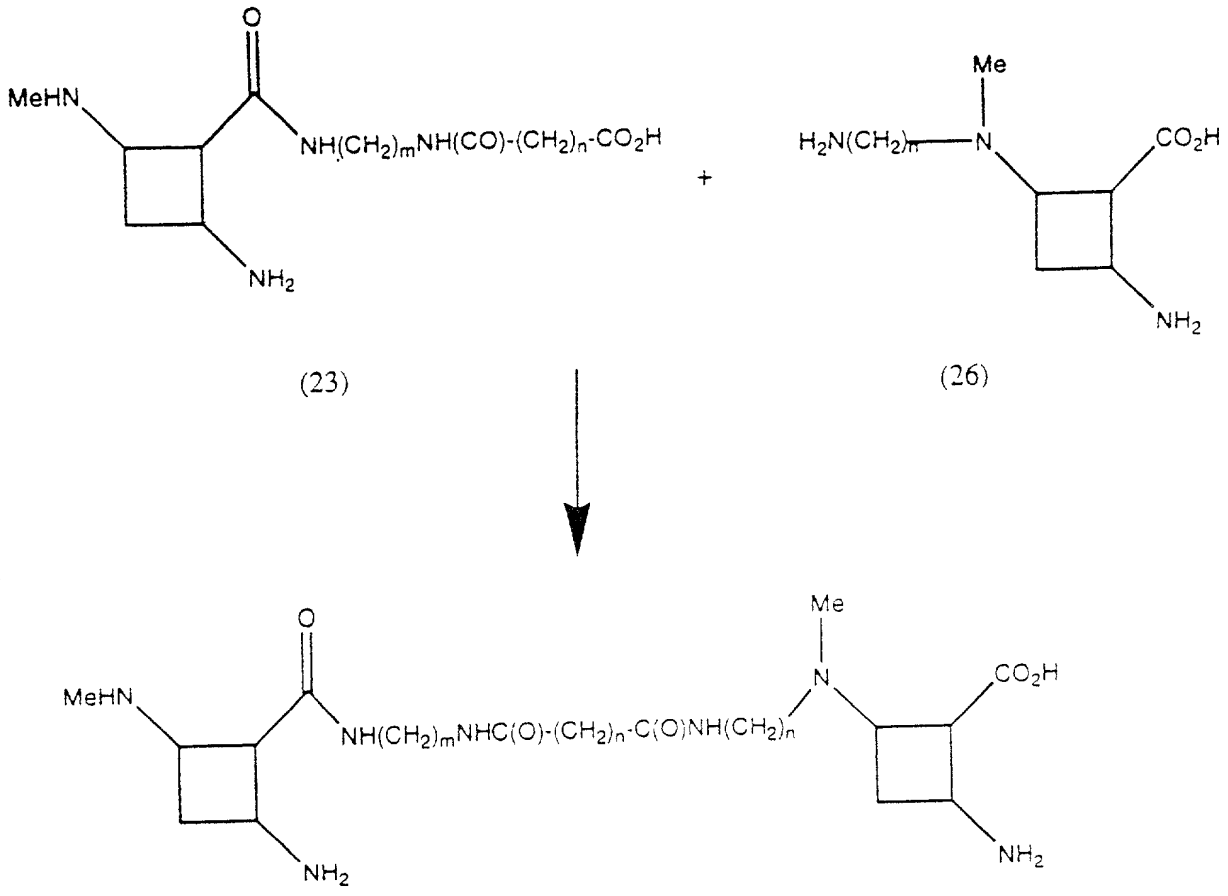


(26)

FIGURE 8

EP 0 955 294 A2

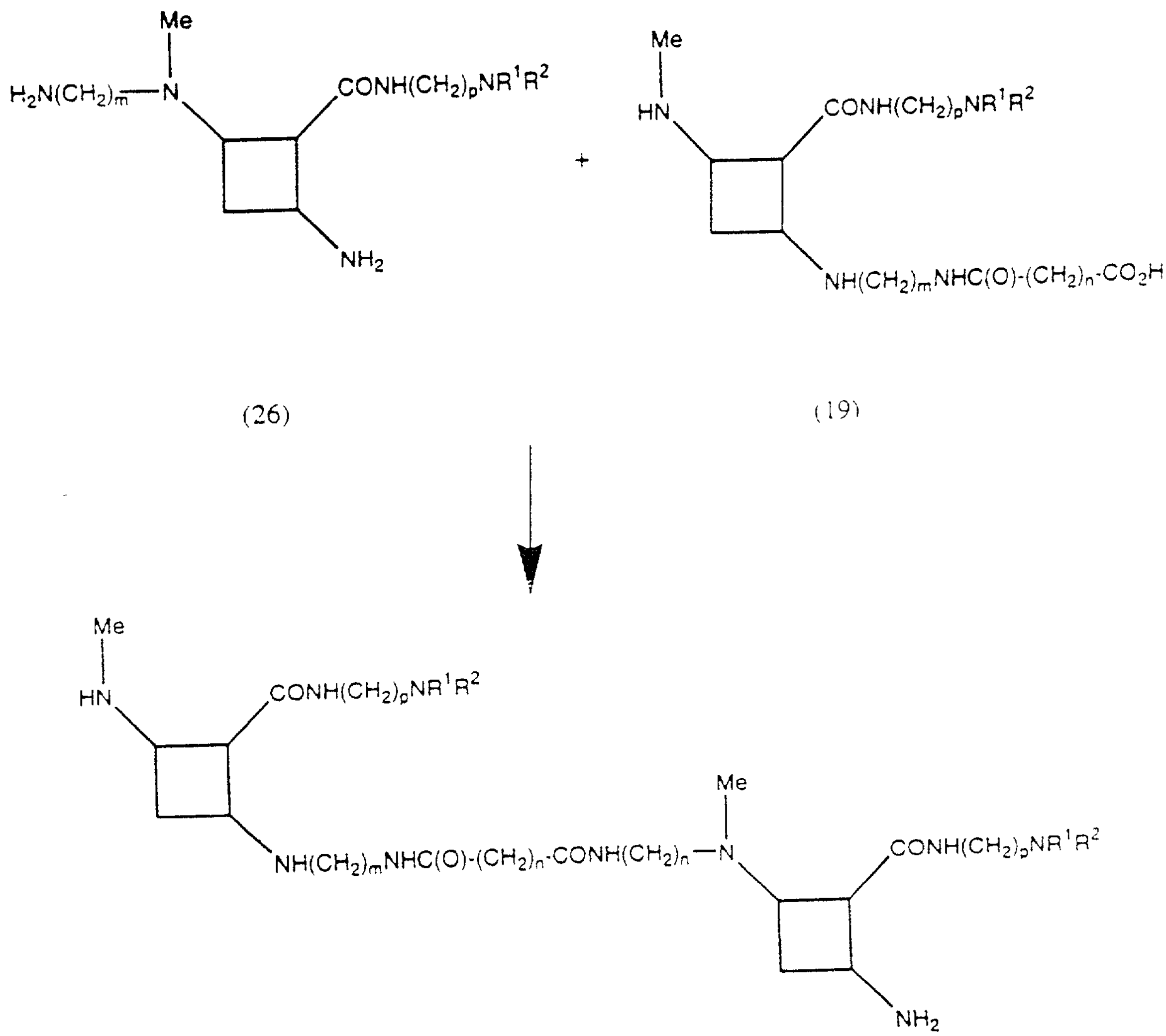
REACTION SCHEME 10



Formula I

FIGURE 9

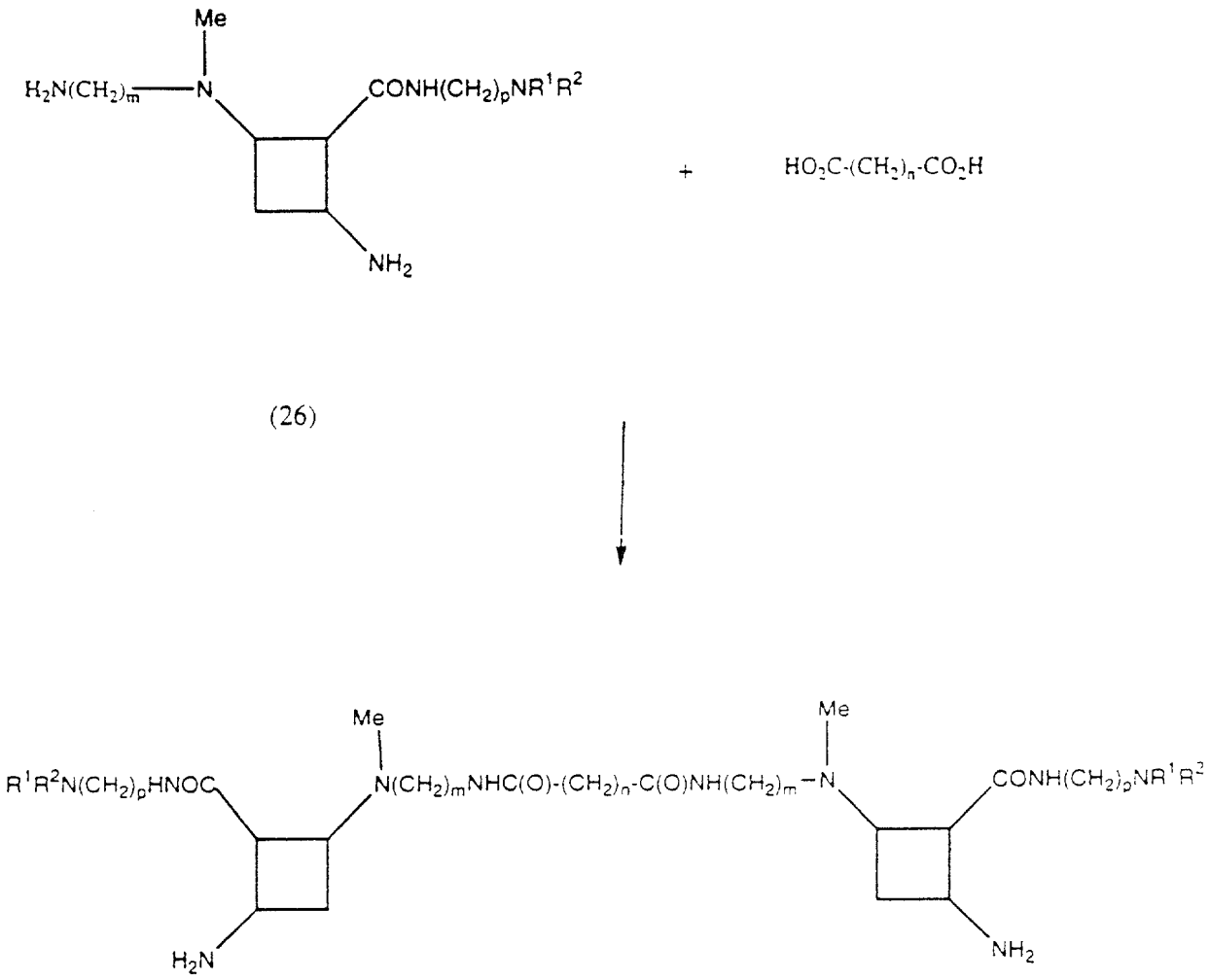
REACTION SCHEME 11



Formula I

FIGURE 10

REACTION SCHEME 12



Formula I

FIGURE 11

Examples of dimeric display

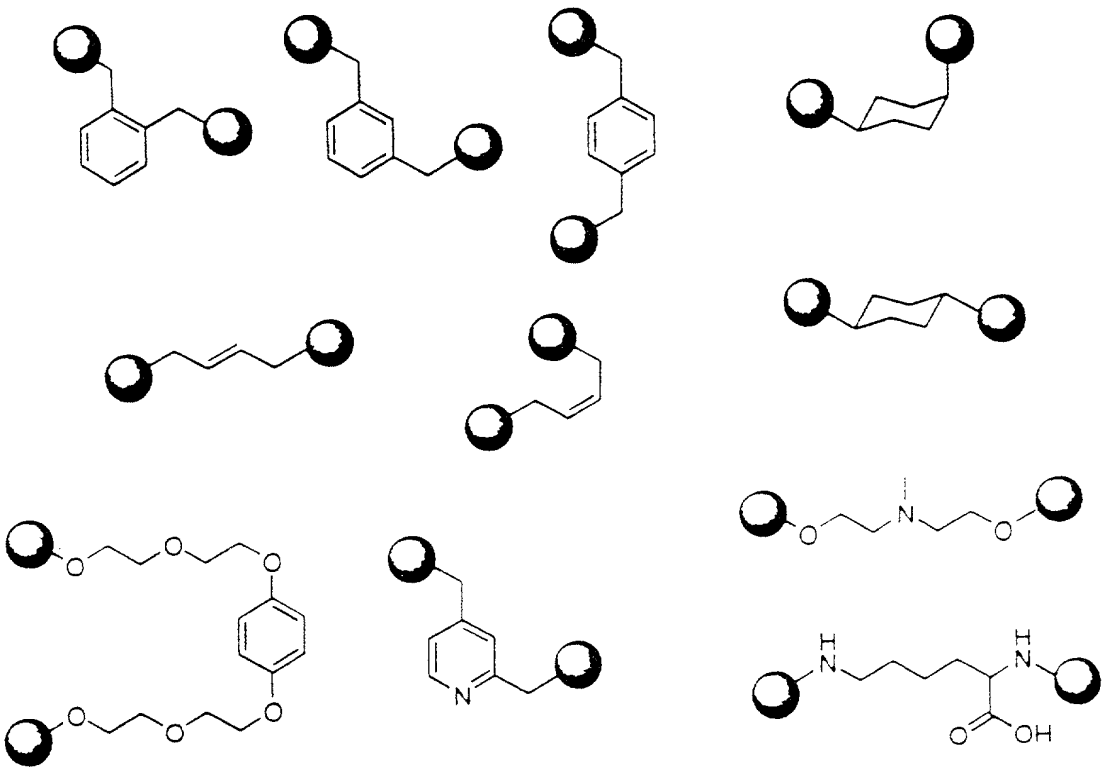


FIGURE 12

PCT/EP2004/010754

Examples of trimeric display

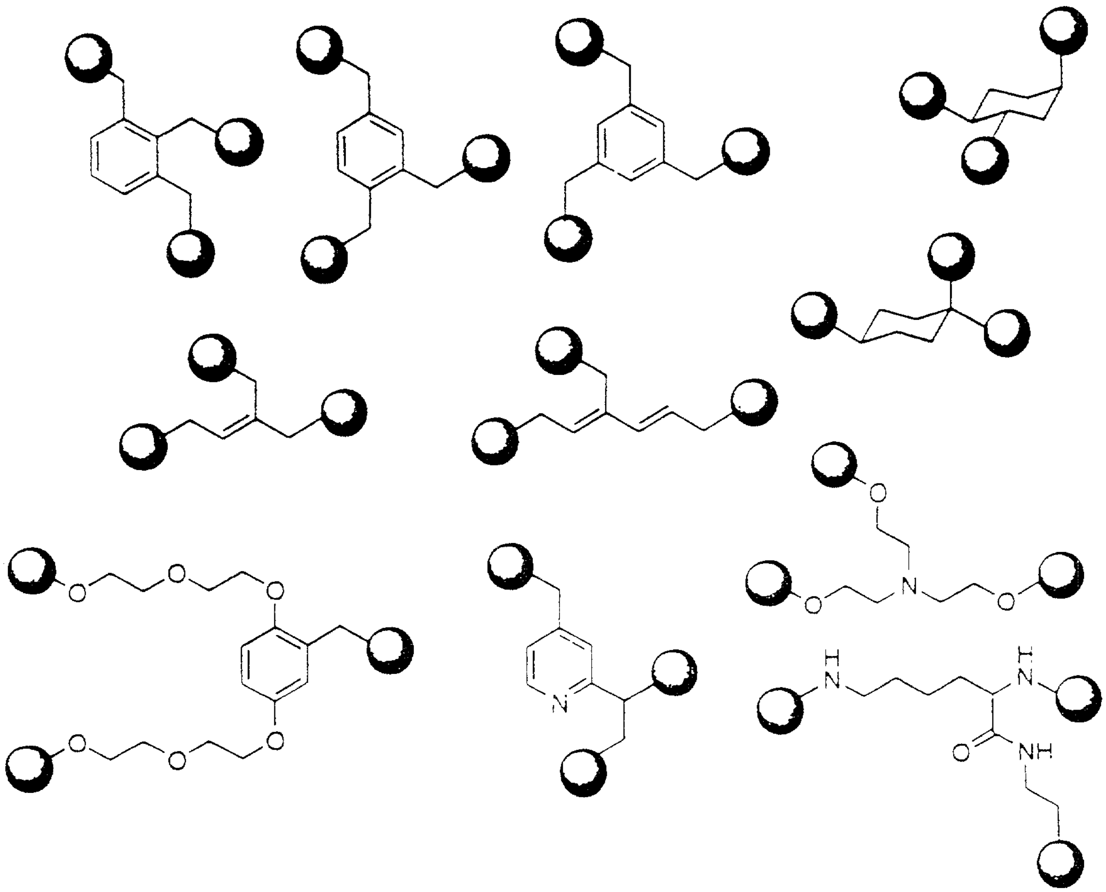


FIGURE 13

Examples of tetrameric display

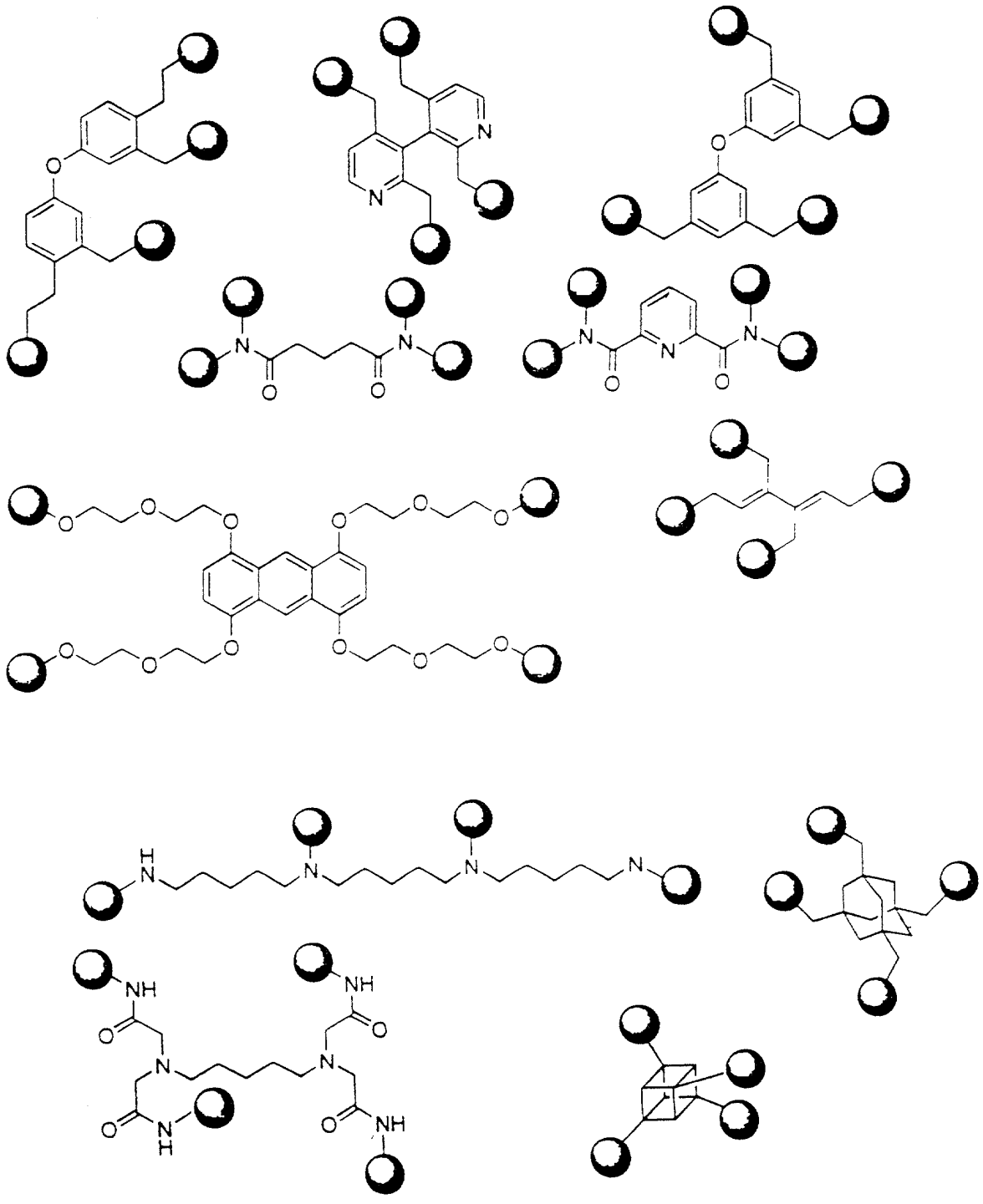


FIGURE 14

Examples of higher order polyvalent display

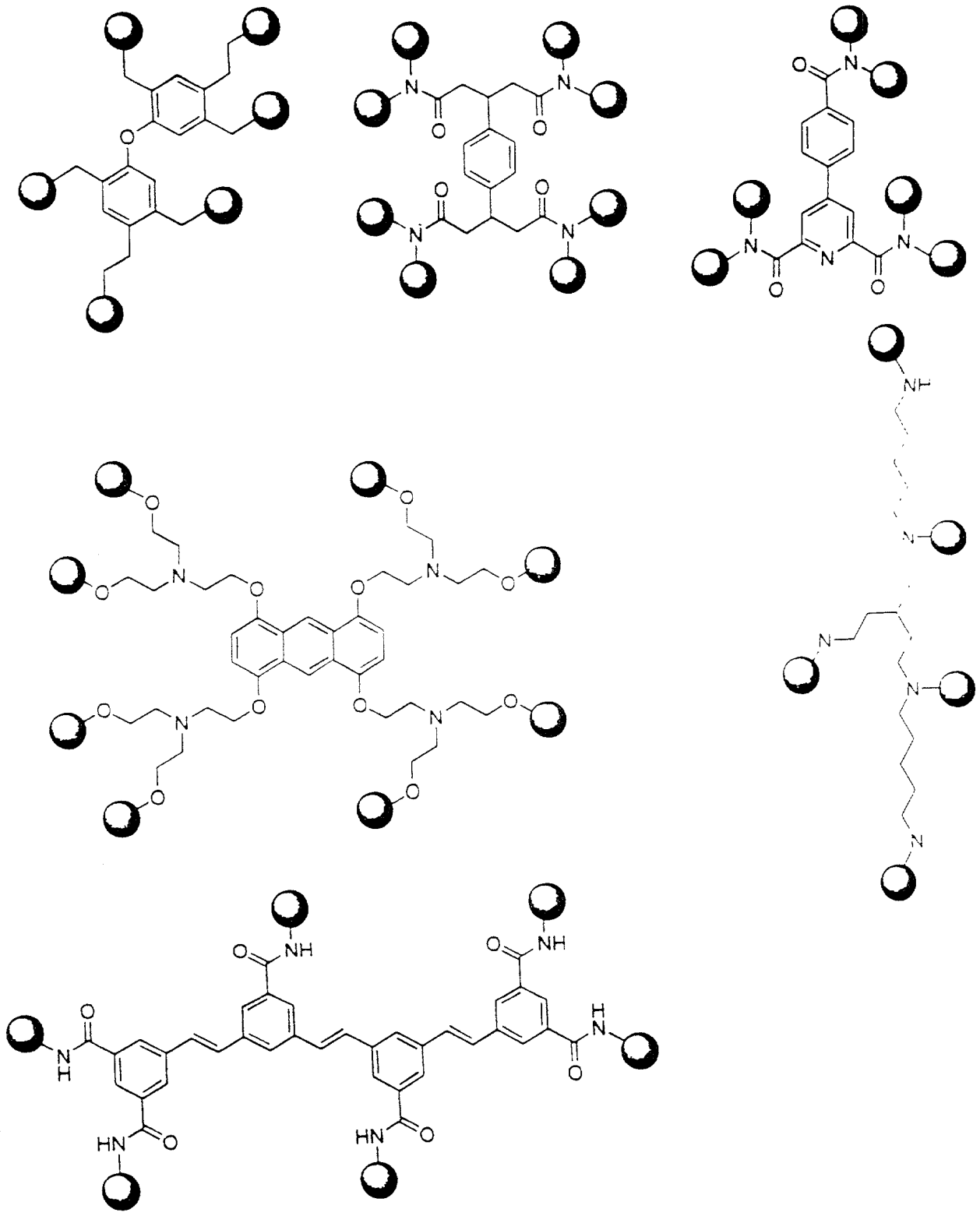
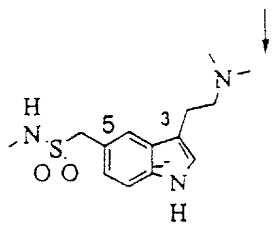
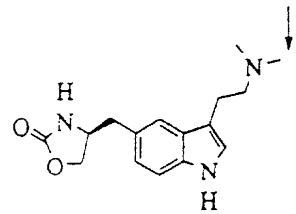


FIGURE 15

C3 SUBSTITUENT

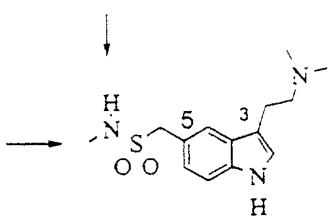


SUMATRIPTAN

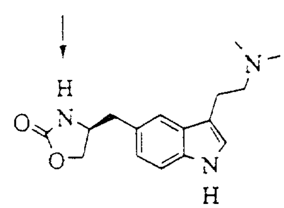


ZOLMITRIPTAN

C5 SUBSTITUENT



SUMATRIPTAN

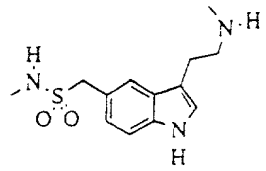


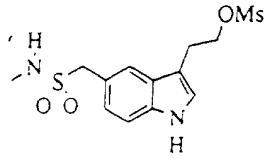
ZOLMITRIPTAN

FIGURE 16

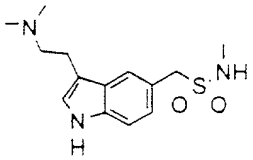
SUMATRIPTAN BUILDING BLOCKS

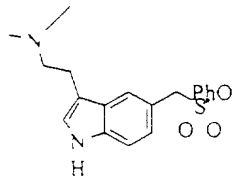
C3PharmacophoricBuilding Blocks



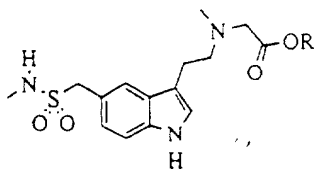


C5PharmacophoricBuilding Blocks





Pharmacophoric Building Blocks that contain a Spacer



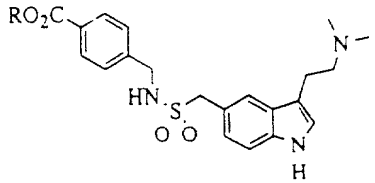
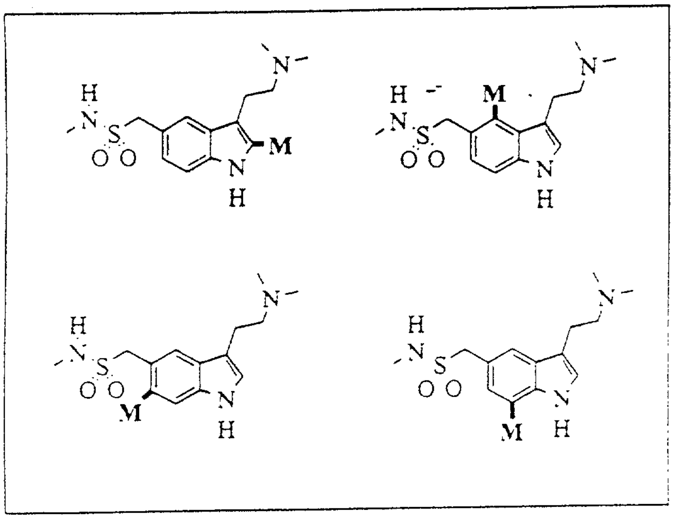
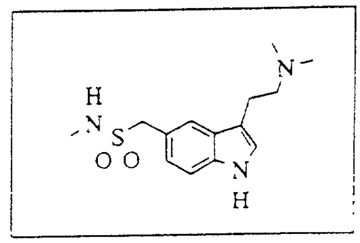


FIGURE 17

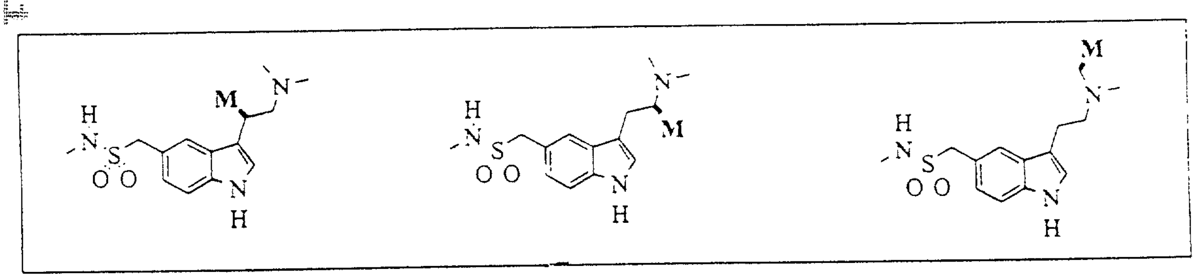
MULTIVALOMERS OF SUMATRIPTAN

1. The Indole Core





2. C3 Substituent



3. C5 Substituent

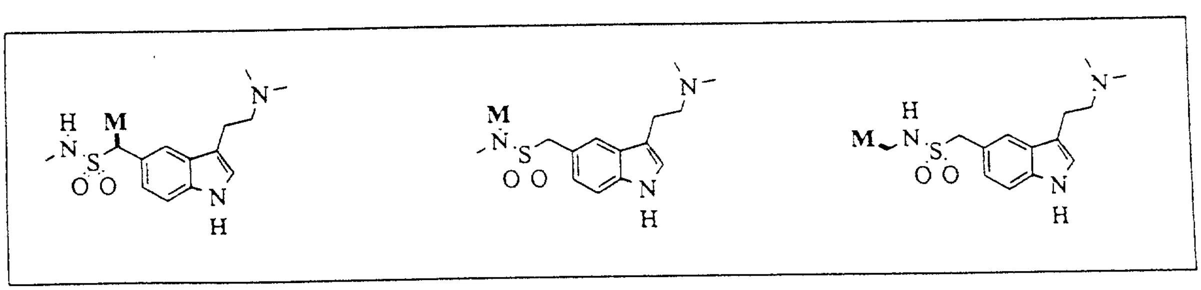
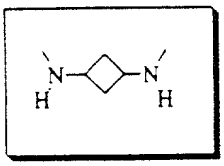
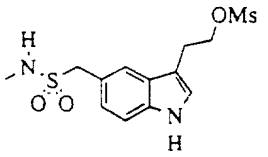


FIGURE 18

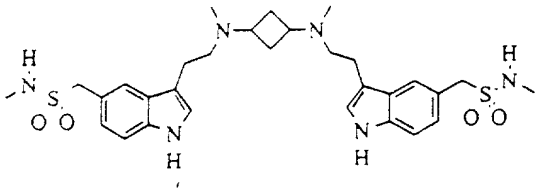
C3 ELECTROPHILE TO PROVIDE MULTIVALOMERS



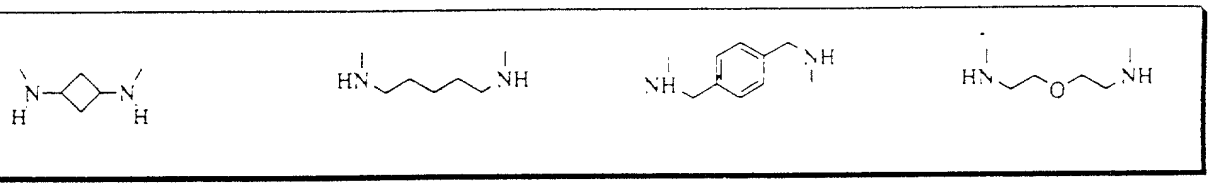


SYNTHESIS

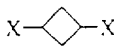
(a)

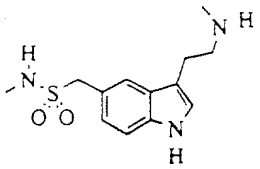


(a) $CHCl_3$, pyridine

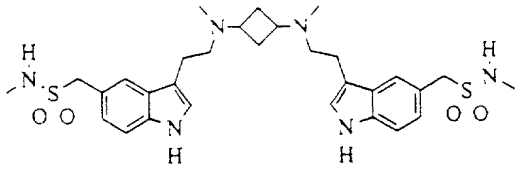


C3 NUCLEOPHILE TO PROVIDE MULTIVALOMERS





(a)



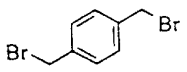
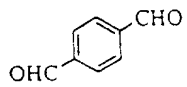
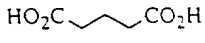
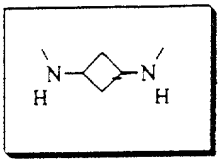
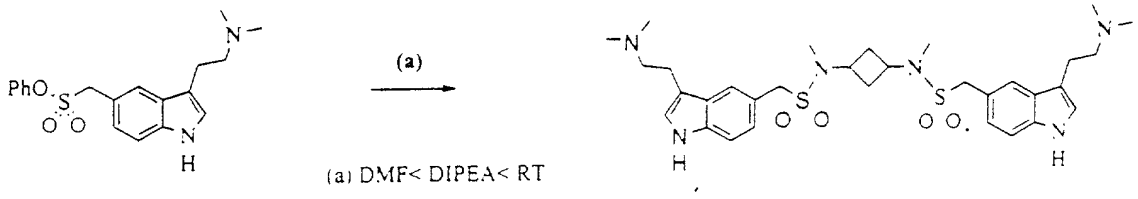
X = -CH_2Br	(a) DCM, pyrdine	
X = -CHO	(a) DCM, $NaBH(OAc)_3$, AcOH	
X = -CO_2H	(a) DIC, DIPEA, DMF	

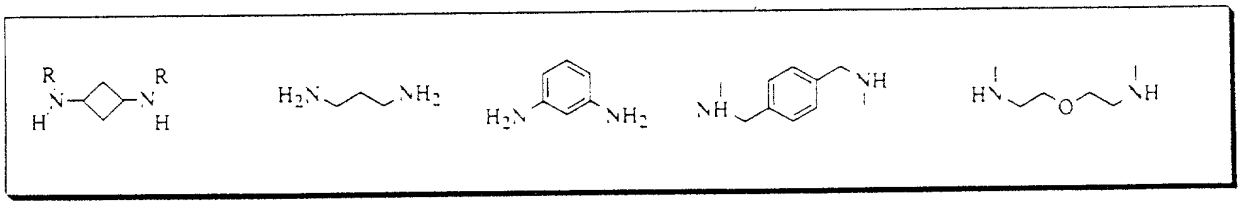
FIGURE 19

C5 FUNCTIONALIZATION OF SUMATRIPTAN

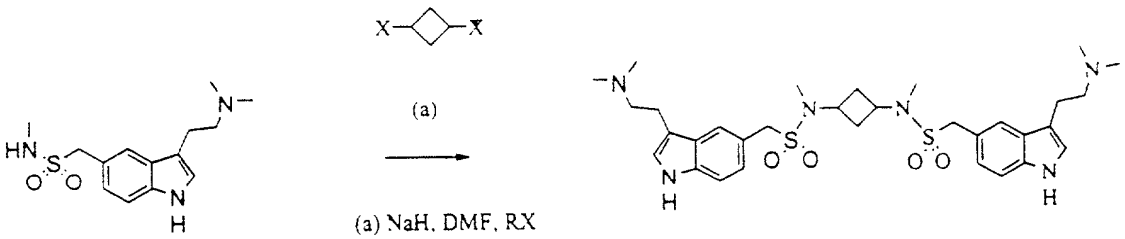
Electrophilic Pharmacophoric Monovalomer







Nucleophilic Pharmacophoric Monovalomer



X = -CH_2Br

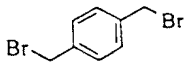
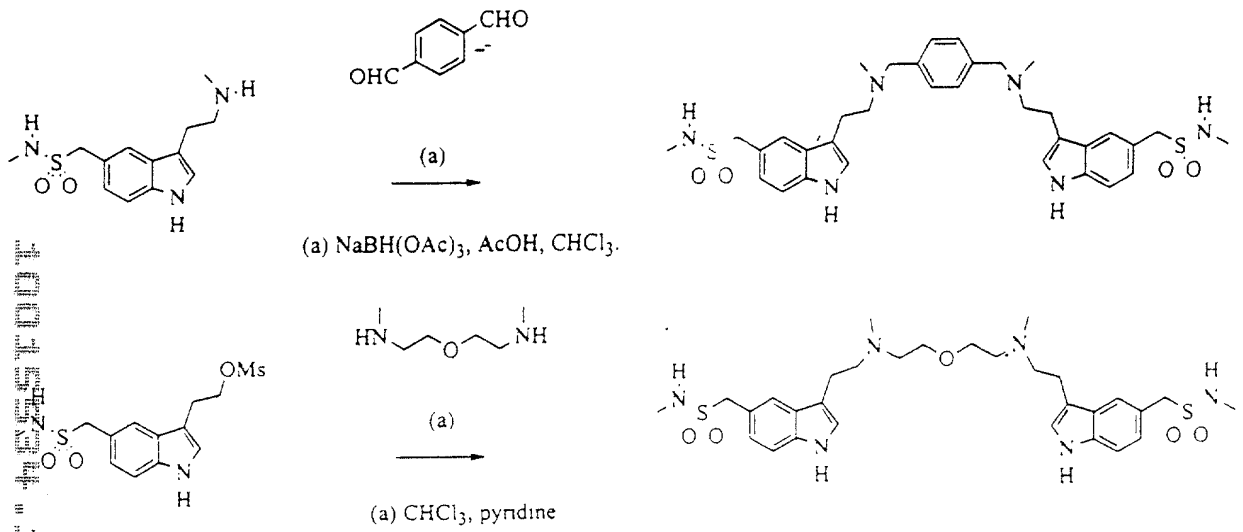


FIGURE 20

SUMATRIPTAN SPECIFICS

C3 Mu,tivalomers



C5 Multivalomers

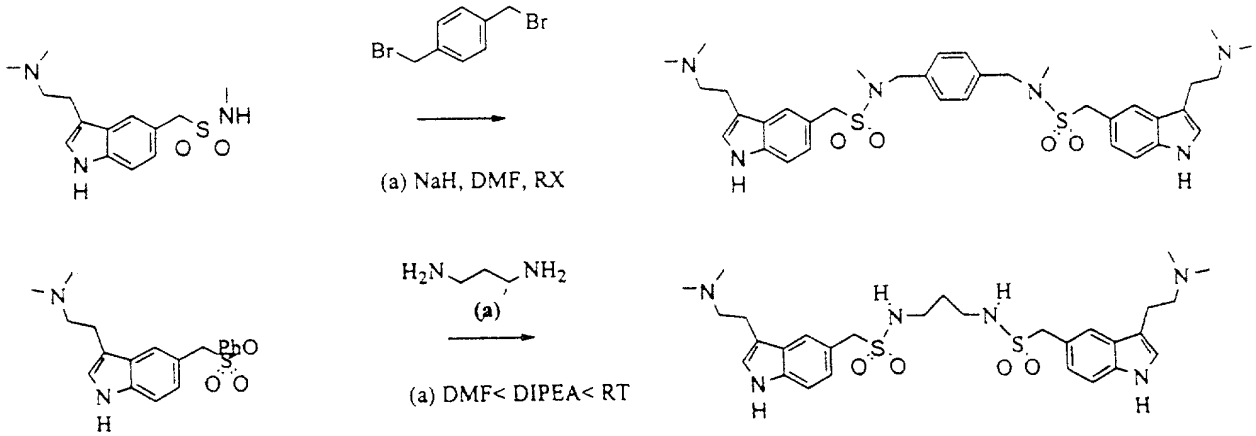
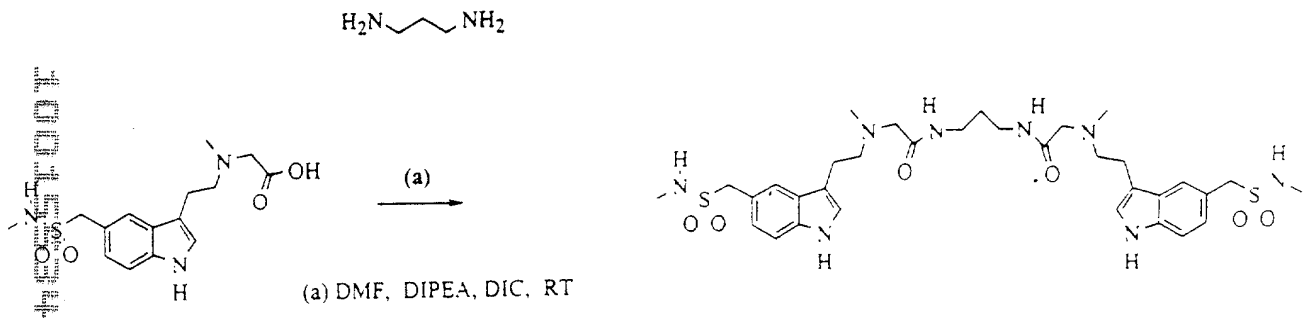


FIGURE 21

SUMATRIPTAN SPACERS

C3 Acid Spacer



C5 Acid Spacer

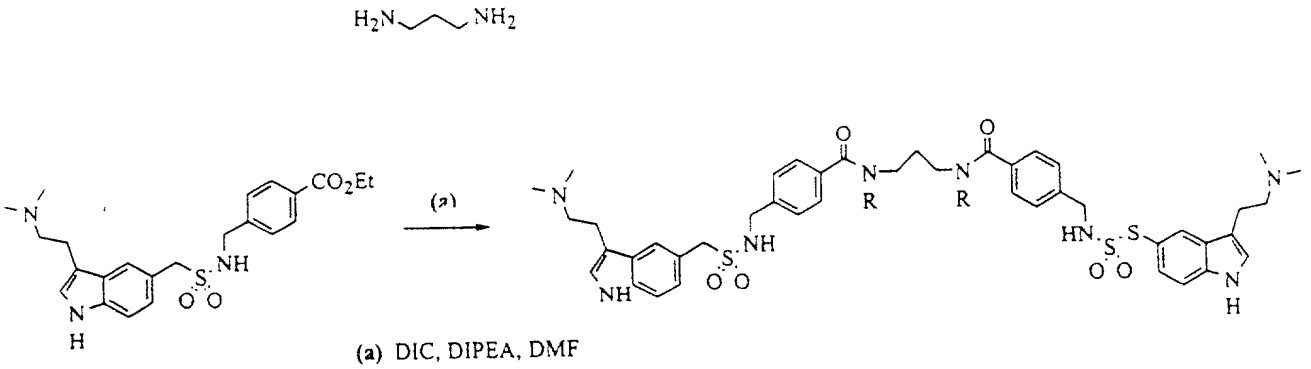
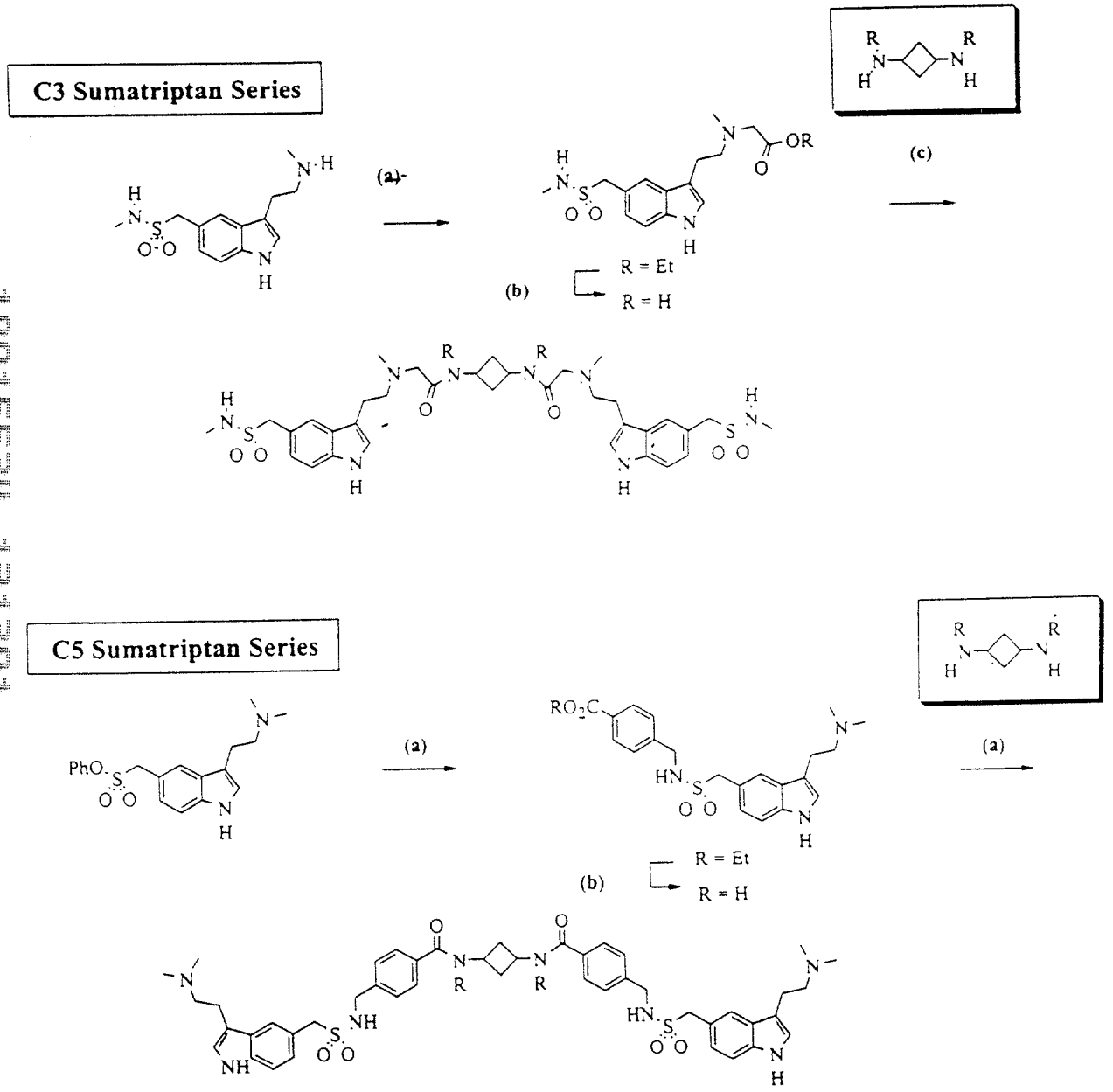


FIGURE 22

Introduction of Spacer To Faciliate Multivalomer Formation



(a) DIPEA, DCM, $BrCH_2CO_2Et$ **(b)** LiOH, THF, H_2O. **(c)** DIC, DIPEA, DMF

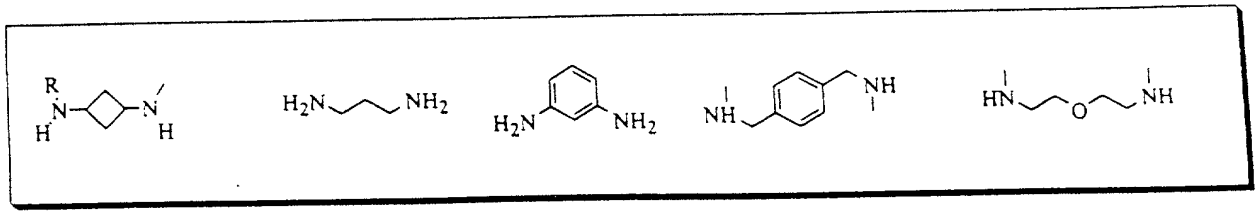
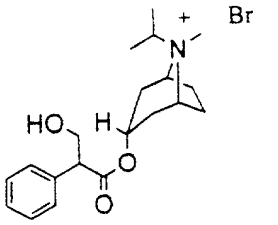
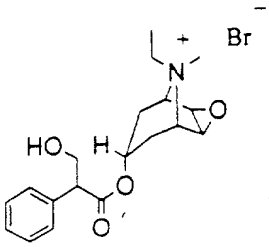


FIGURE 23

MUSCARINIC ANTAGONISTS USED IN AIRWAY DISEASE

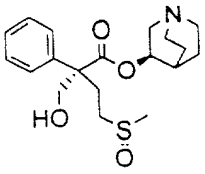


IPRATROPIUM BROMIDE

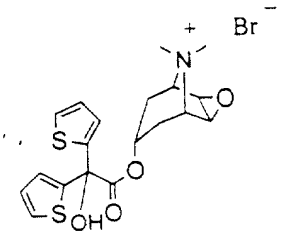


OXITROPIUM BROMIDE

i) Airway disease



REVATROPATE



TIOTROPIUM BROMIDE

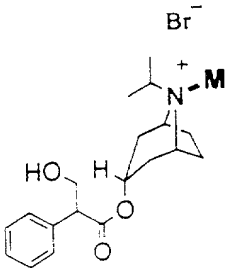
FIGURE 24

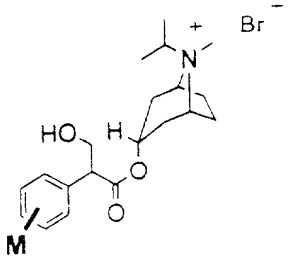
SITES FOR DIMERIZATION

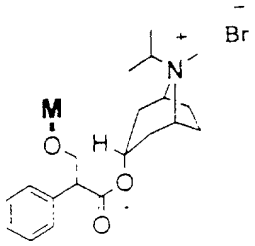
Nitrogen Atom of Tropane Core

Aromatic Ring

Primary Hydroxyl



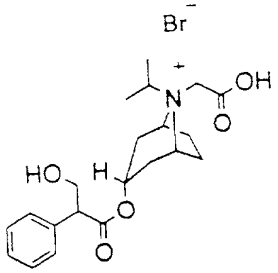


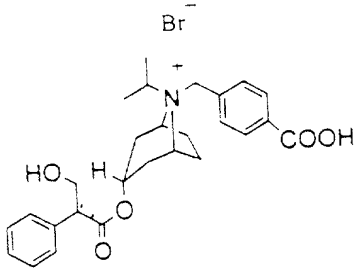


Suitable Pharmacophoric Building Blocks

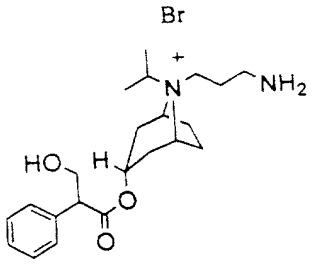
Nitrogen Atom of Tropane Core

Acid Series





Amine Series



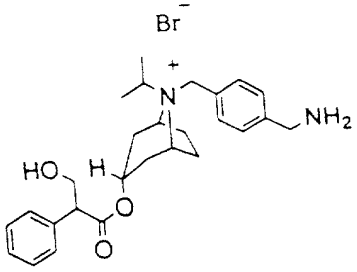
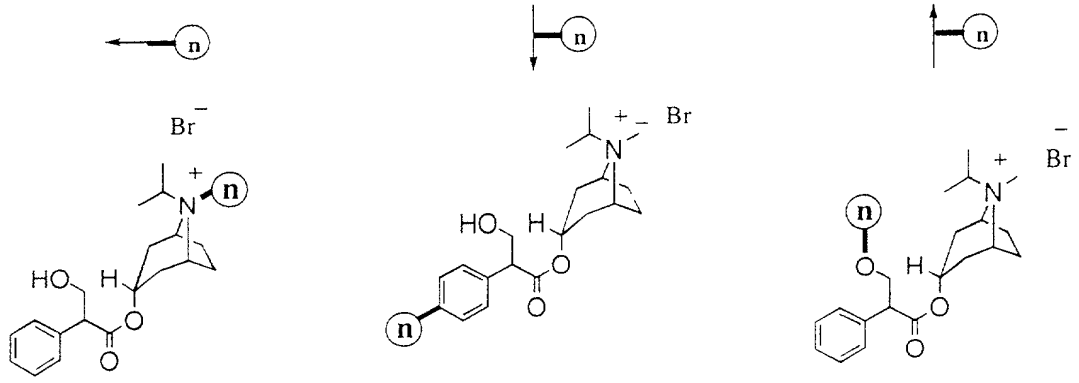


FIGURE 25

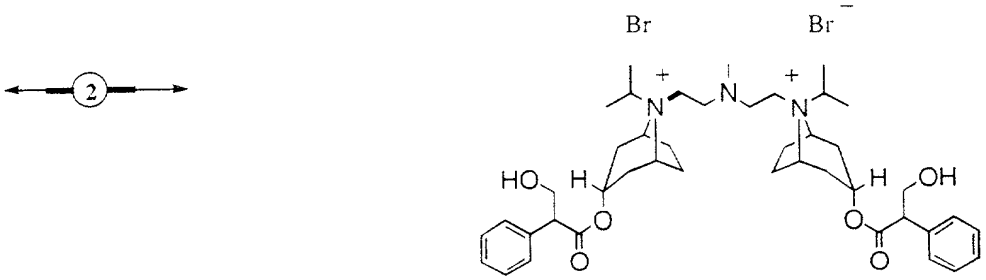
Ipratropium Multivalomers 1-Different Points of Attachment

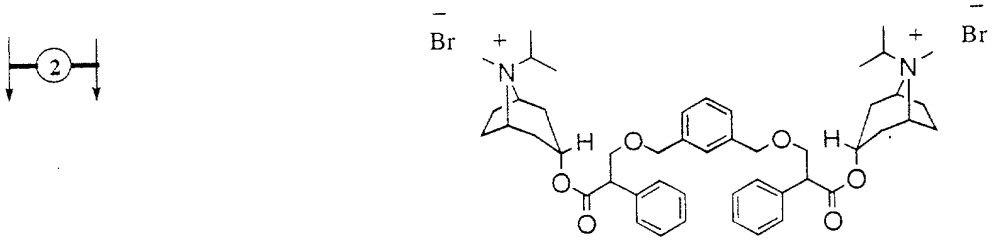


n defines the valency of the multivalomer

◯ defines the framework core

⟶ distinguishes the differing points of attachment of ipratropium





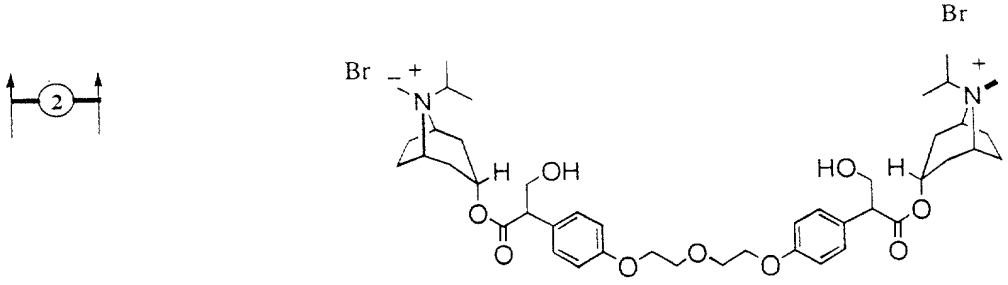
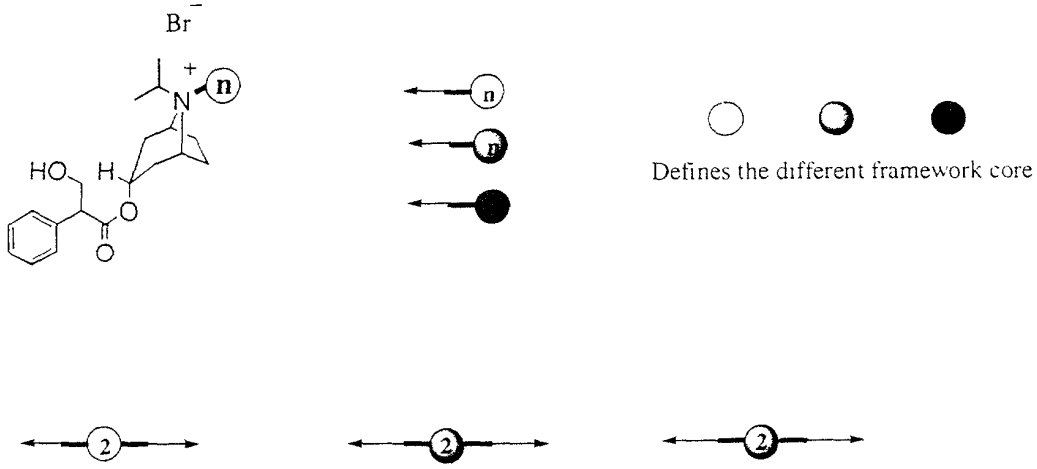


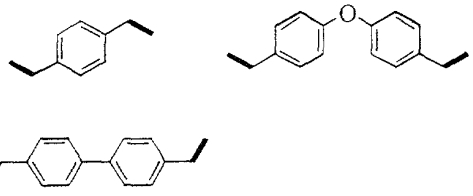
FIGURE 26

Ipratropium Multivalomers 2-Alternative Framework Cores

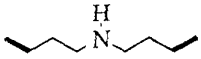


1. Alkyl Series

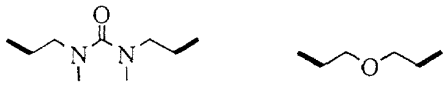
2. Aromatic Series



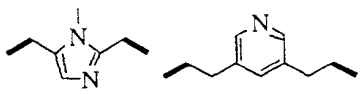
3. H-bond donor



4. H bond acceptor



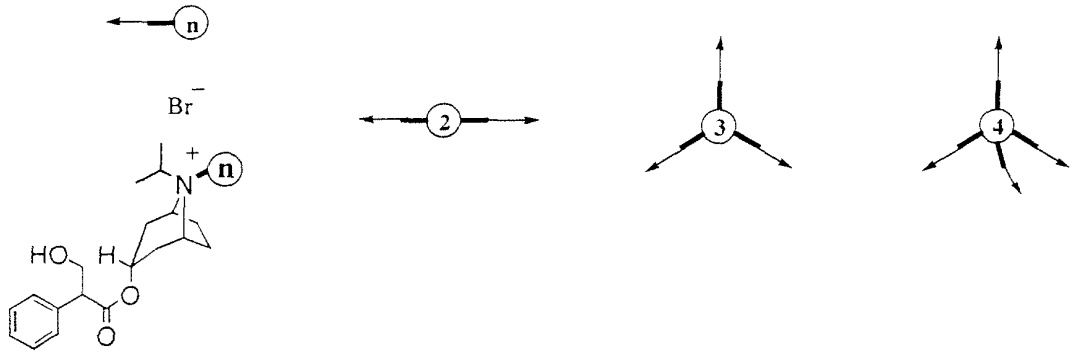
5. Basic



6. Acidic

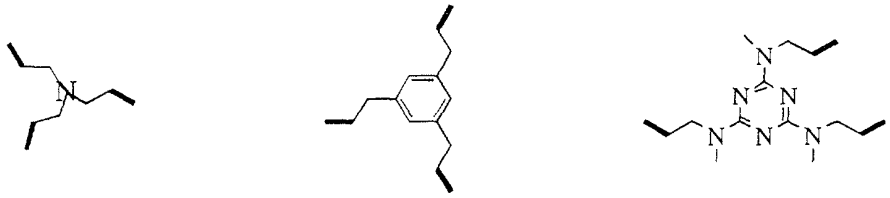
FIGURE 27

Ipratropium Multivalomers 3-Alternative Framework Valency



Dimeric Series

Trimeric Series



Tetrameric Series

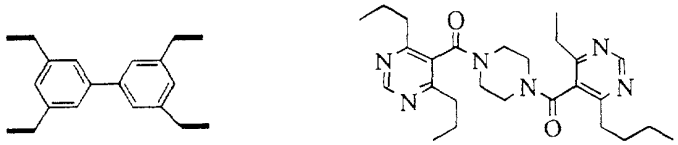


FIGURE 28

Ipratropium Multivalomers 4-Relative Pharmacophore Orientation

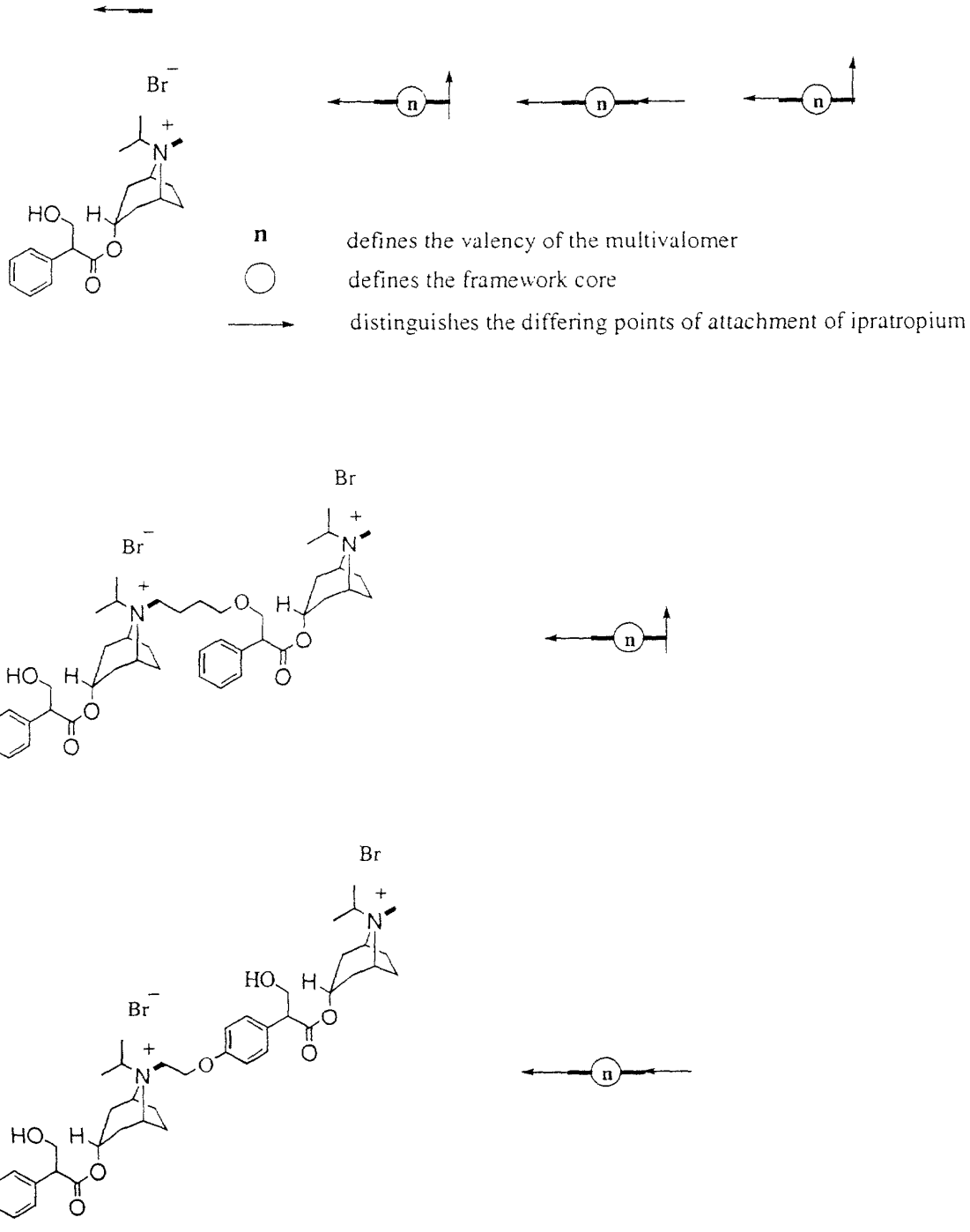
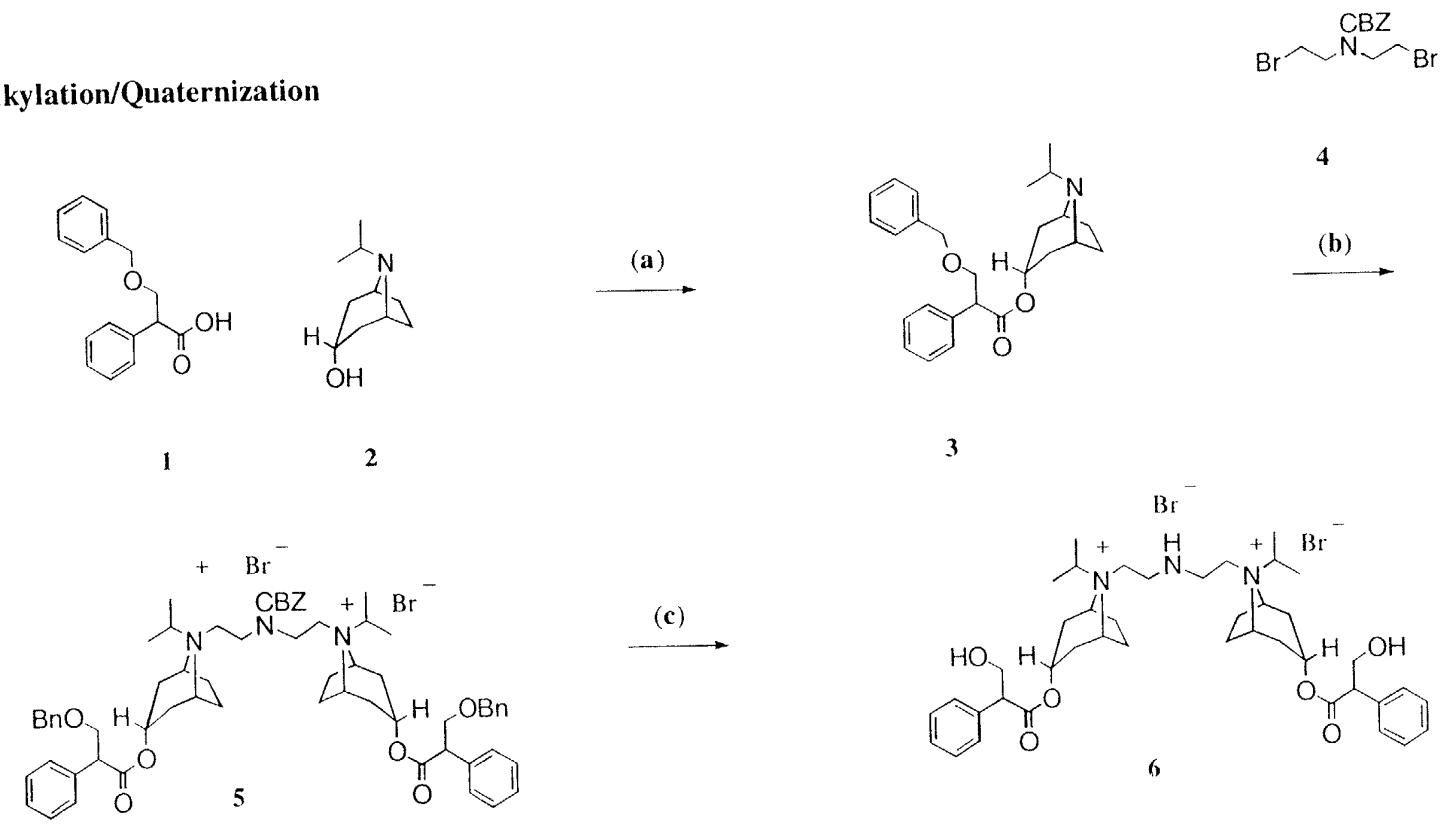


FIGURE 29

POETAT"hCSSPOOT

IPRATROPIUM 1-N-Linked Multivalomers

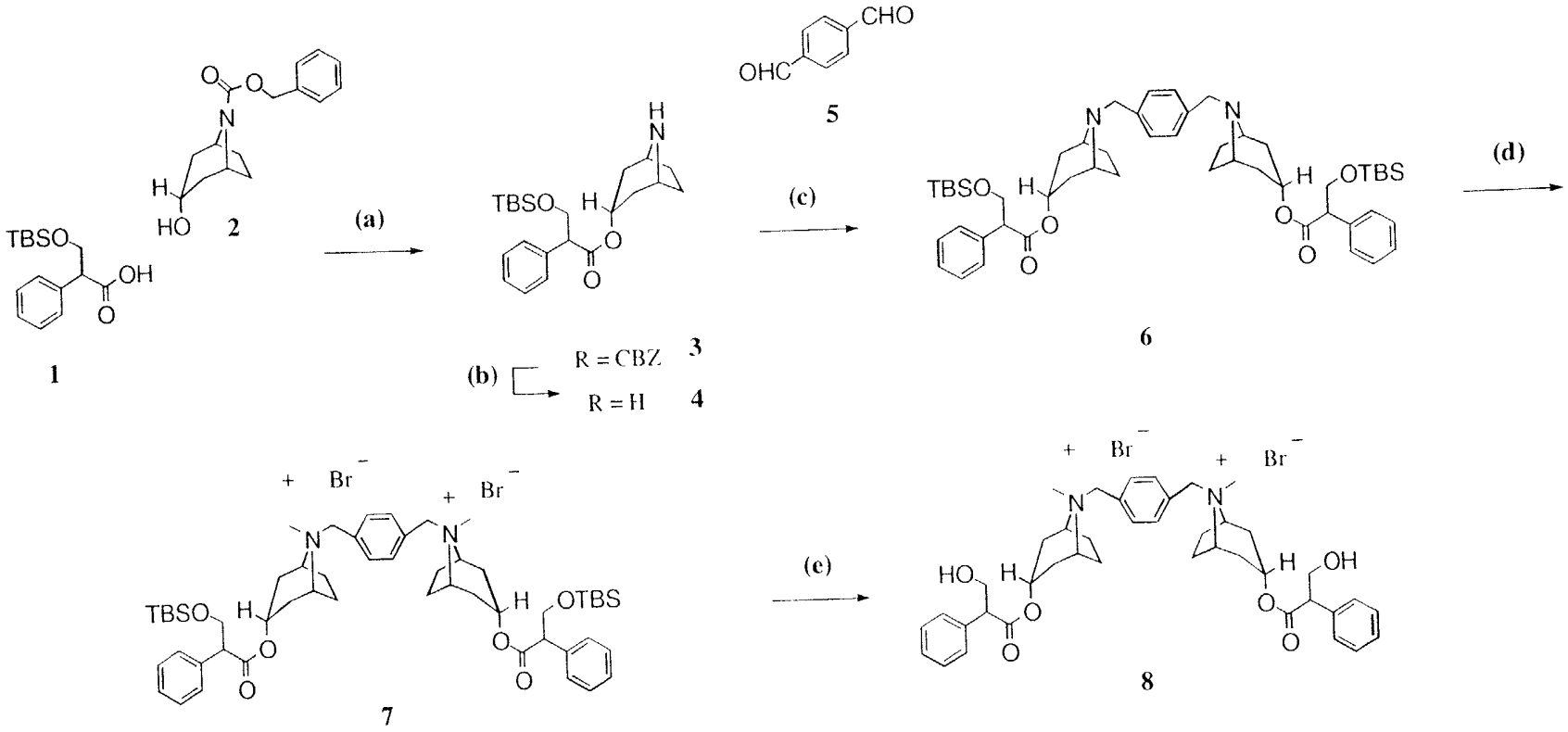
1. Alkylation/Quaternization



(a) DIC, DMAP, DMF (b) $CHCl_3$ (c) Pd/C, H_2, EtOAc.

FIGURE 30

1. Reductive Amination/Quaternization

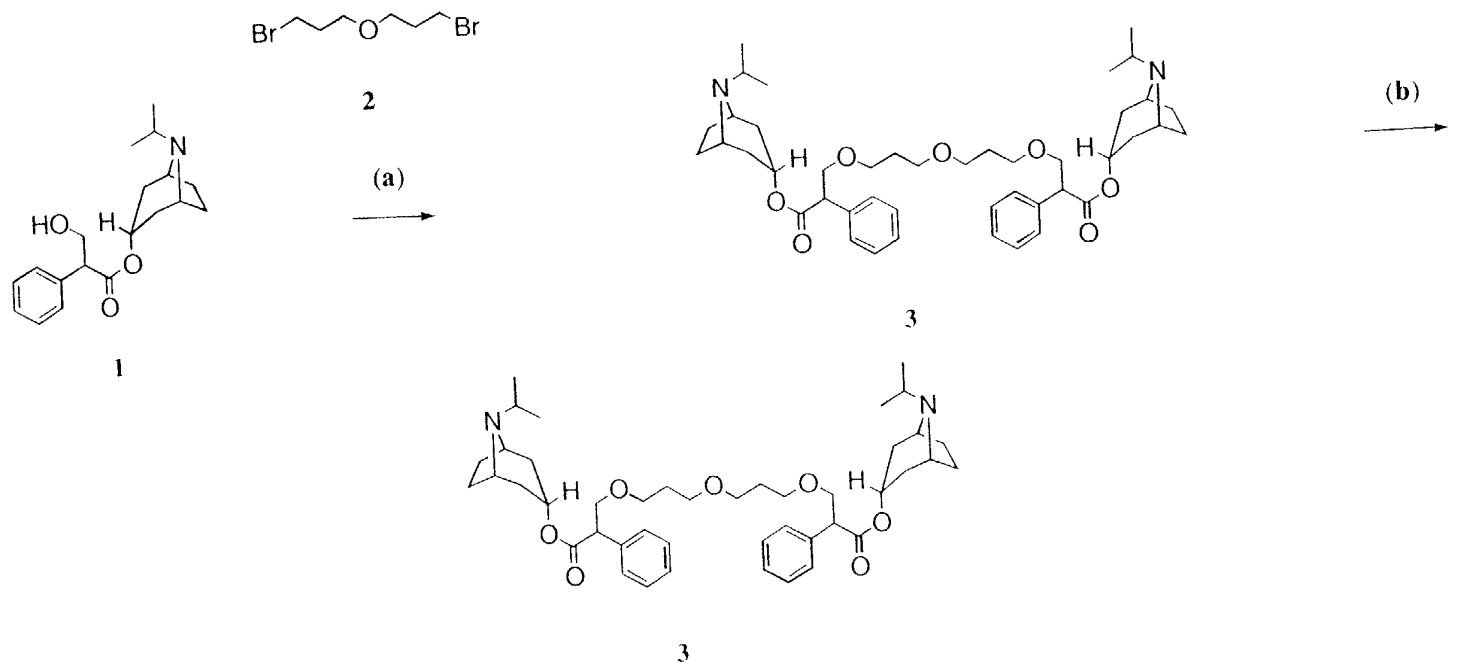


(**a**) DIC, DMF, DMF (**b**) Pd/C, H_2, EtOAc (**c**) $NaBH(OAc)_3$, $CHCl_3$, AcOH (**d**) MeBr, $CHCl_3$ (**e**) TBAF, THF

FIGURE 31

TOCTAT "HESSTOOT

IPRATROPIUM 3-O-Linked Multivalomers



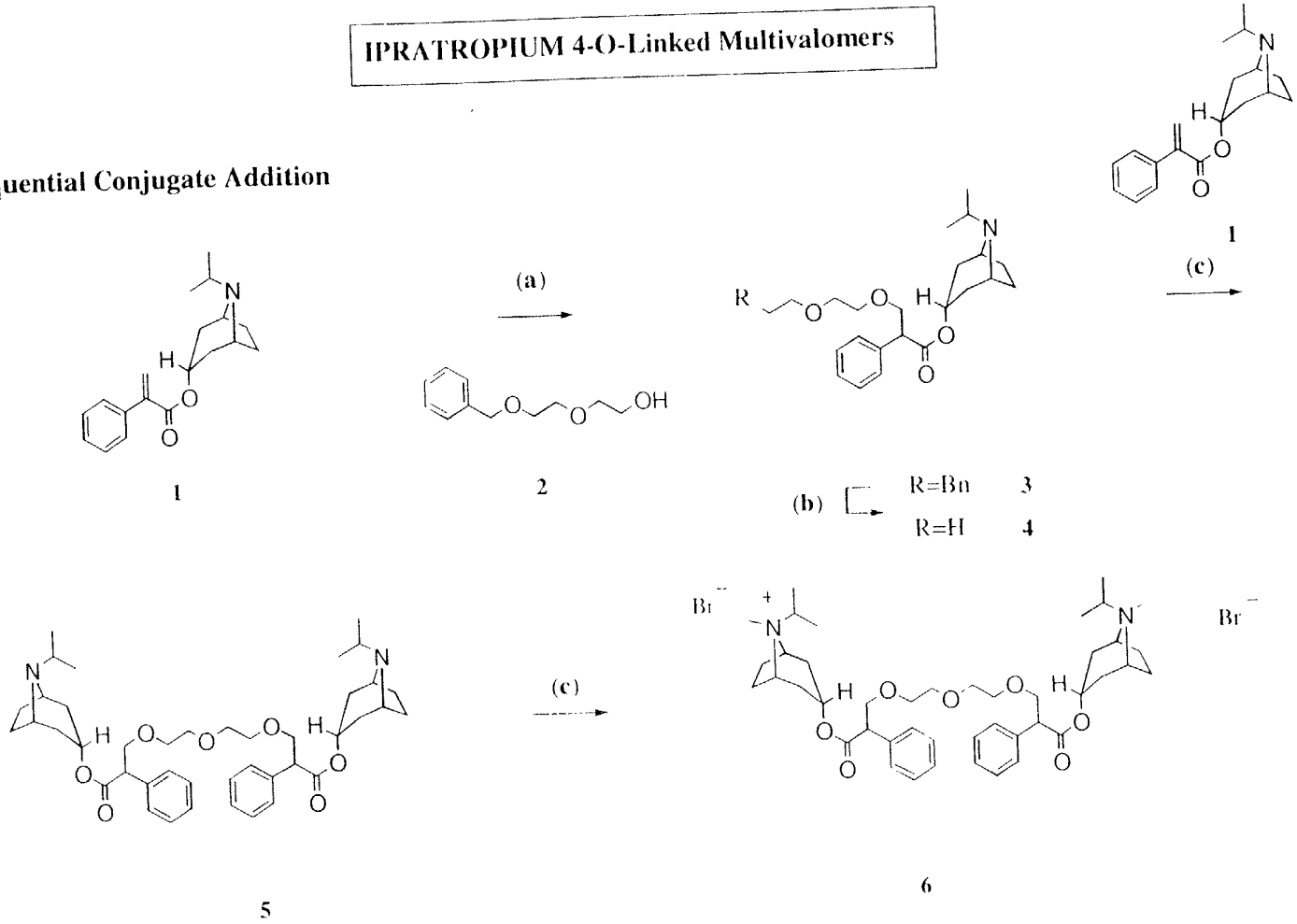
(**a**) NaH, THF (**b**) MeBr, $CHCl_3$, reflux

FIGURE 32

TOETZT'HESSTOOT

IPRATROPIUM 4-O-Linked Multivalomers

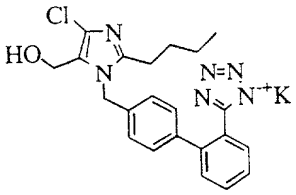
Sequential Conjugate Addition



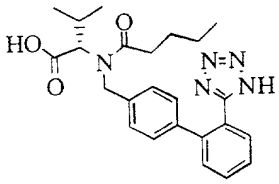
(a) NaH, DME, heat (b) Pd/C, H_2, EtOAc (c) NaH, DME, heat (d) MeBr, $CHCl_3$, heat

FIGURE 33

AT1 RECEPTOR ANTAGONISTS

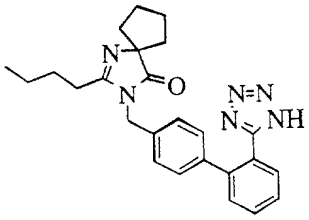


LOSARTAN (Cozaar)
(Dupont Merck)



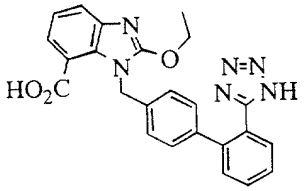
VALSARTAN (Diovan)
(Novartis)

FIGURE 34



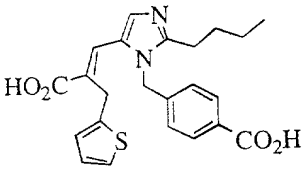
IRBESARTAN

(Sanofi)



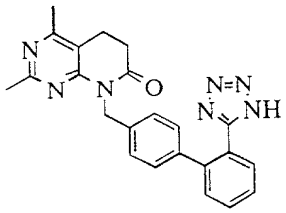
CANDESARTAN (Atacand)

(Takeda)



EPROSARTAN (Tevetan)

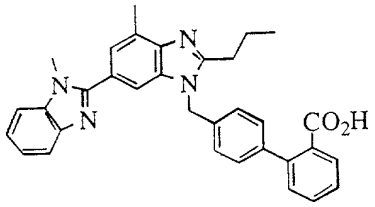
(Smith KlineBeecham)



TASOSARTAN (Verdia)

(Wyerth-Ayerst)

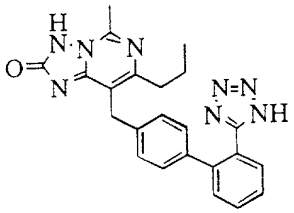
FIGURE 35



TELMISARTAN

(Boehringer Ingelhiem)

Phase III



RIPISARTAN

(Bristol Myers Squibb)

Phase II

Phase II

CS-866 Sankyo

DA-727 Daiichi

KRH-594 Wakunga

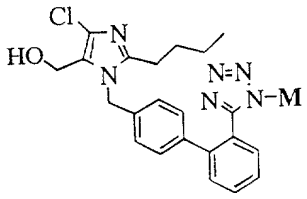
LR-B/081 Lusofarmaco

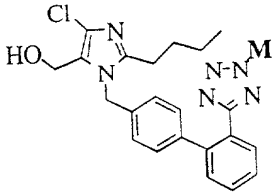
TAK-536 Takeda

YM-358 Yamanouchi

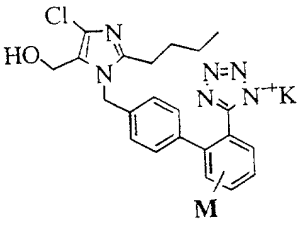
FIGURE 36

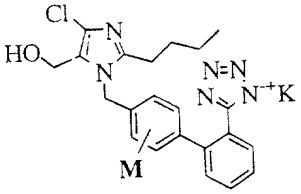
1. Tetrazole

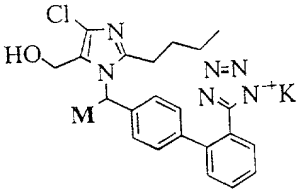




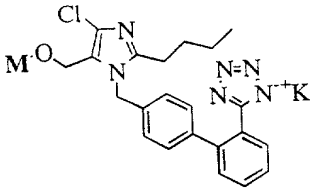
2. Biaryl Motif

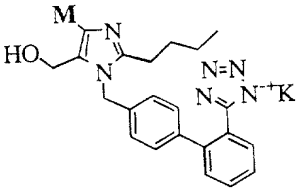






3. Imidazole Substituents





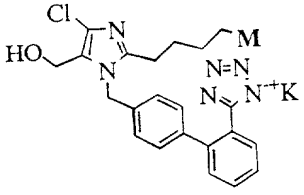
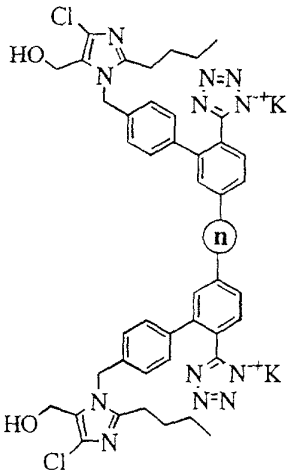
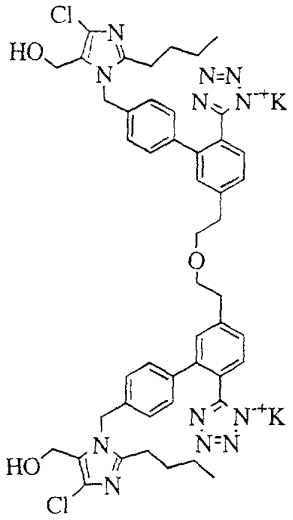


FIGURE 37

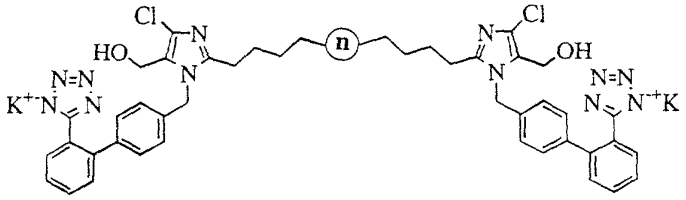
Losartan Multivalomers 1-Differing Points of Attachment

1. Aryl Linked Multivalomers





2. Butyl Linked Multivalomers



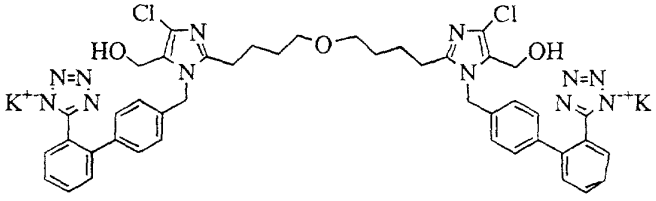
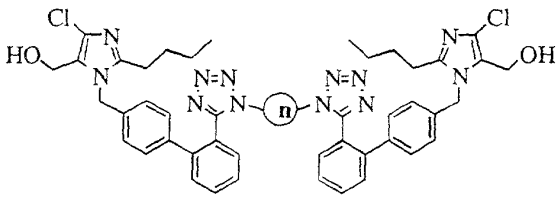
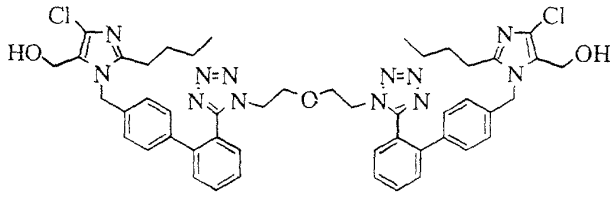


FIGURE 38

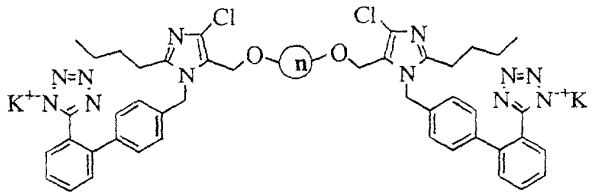
Losartan Multivalomers 1-Differing Points of Attachment

1. Tetrazole Linked Multivalomers





2. Aryl Linked Multivalomers



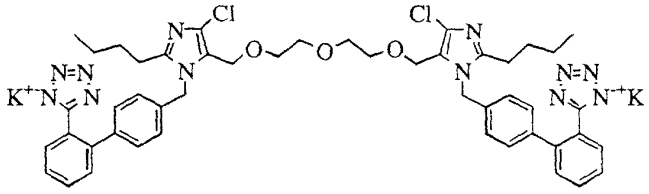
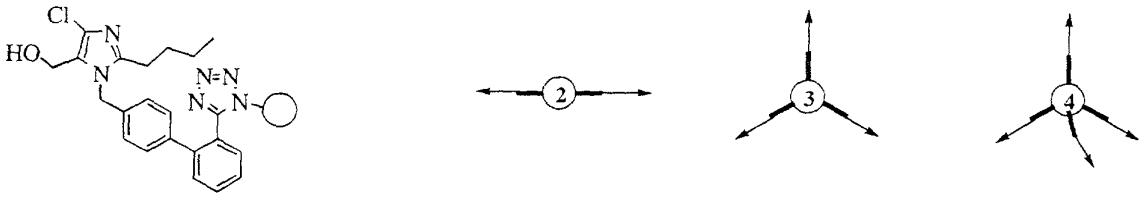


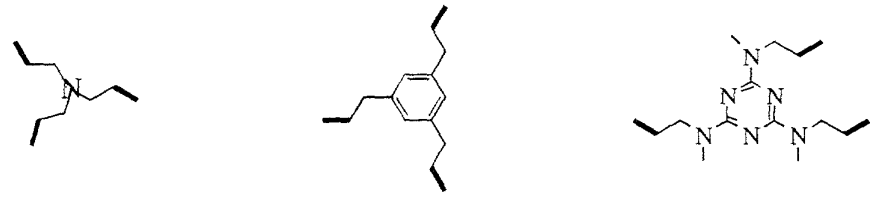
FIGURE 39

Lorsartan Multivalomers 2-Differing Valency of Multivalomer



Dimeric Series

Trimeric Series



Tetrameric Series

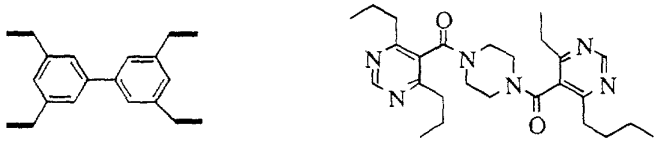
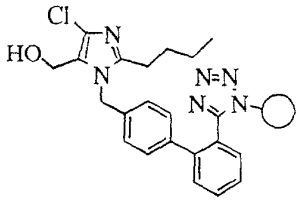
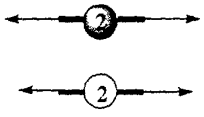


FIGURE 40

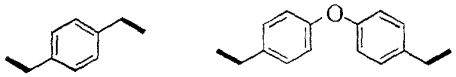
Lorsartan Multivalomers 3-Differing Framework Building Blocks



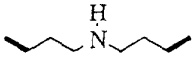


1. Alkyl Series

2. Aromatic Series

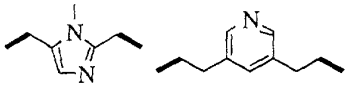


3. H-bond donor



4. H bond acceptor

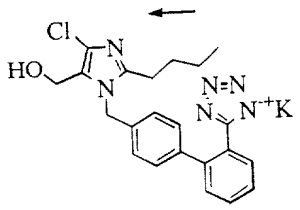
5. Basic

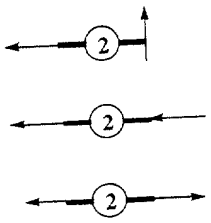


6. Acidic

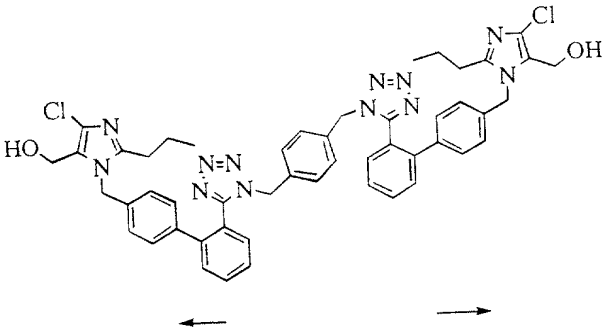
FIGURE 41

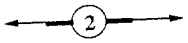
Losartan Multivalomers 4-Different Relative Connectivity

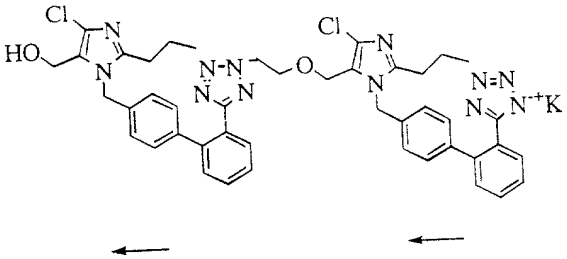


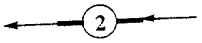


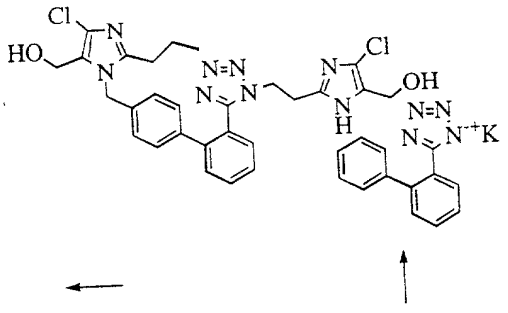
LOSARTAN (Cozaar)











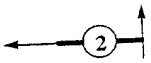
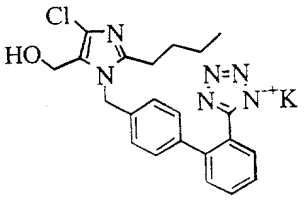
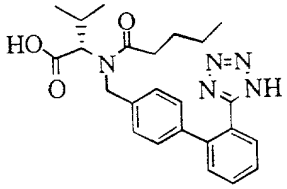


FIGURE 42

Losartan Multivalomers 5-Heterovalomers

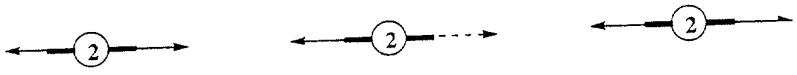


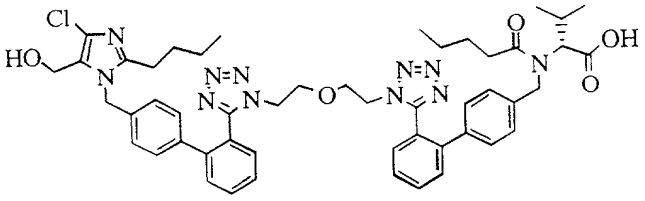
LOSARTAN (Cozaar)



VALSARTAN (Diovan)

Heterovalomers



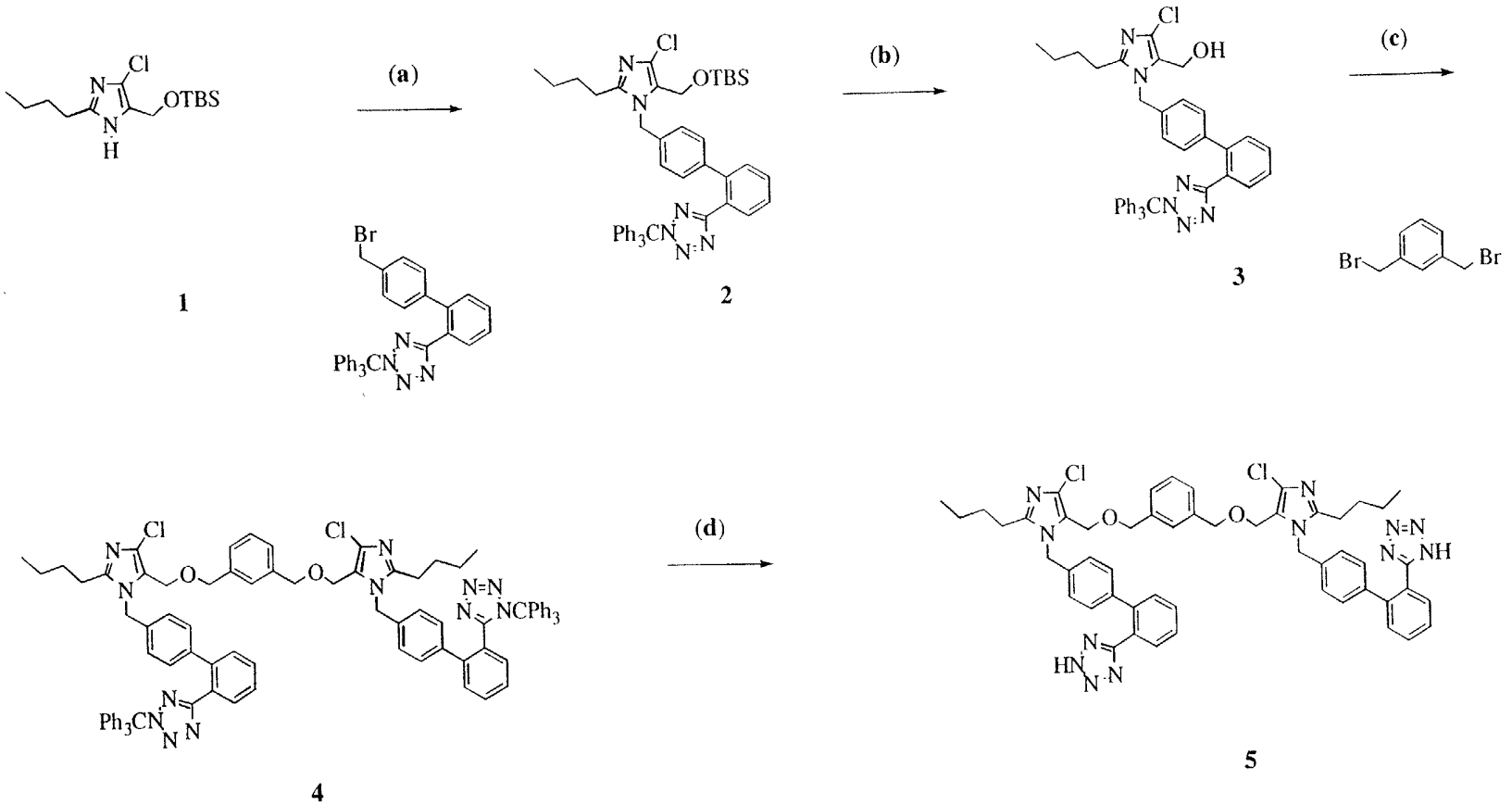


Losartan/Valsartan

FIGURE 43

TOETZT"tESSTOOT

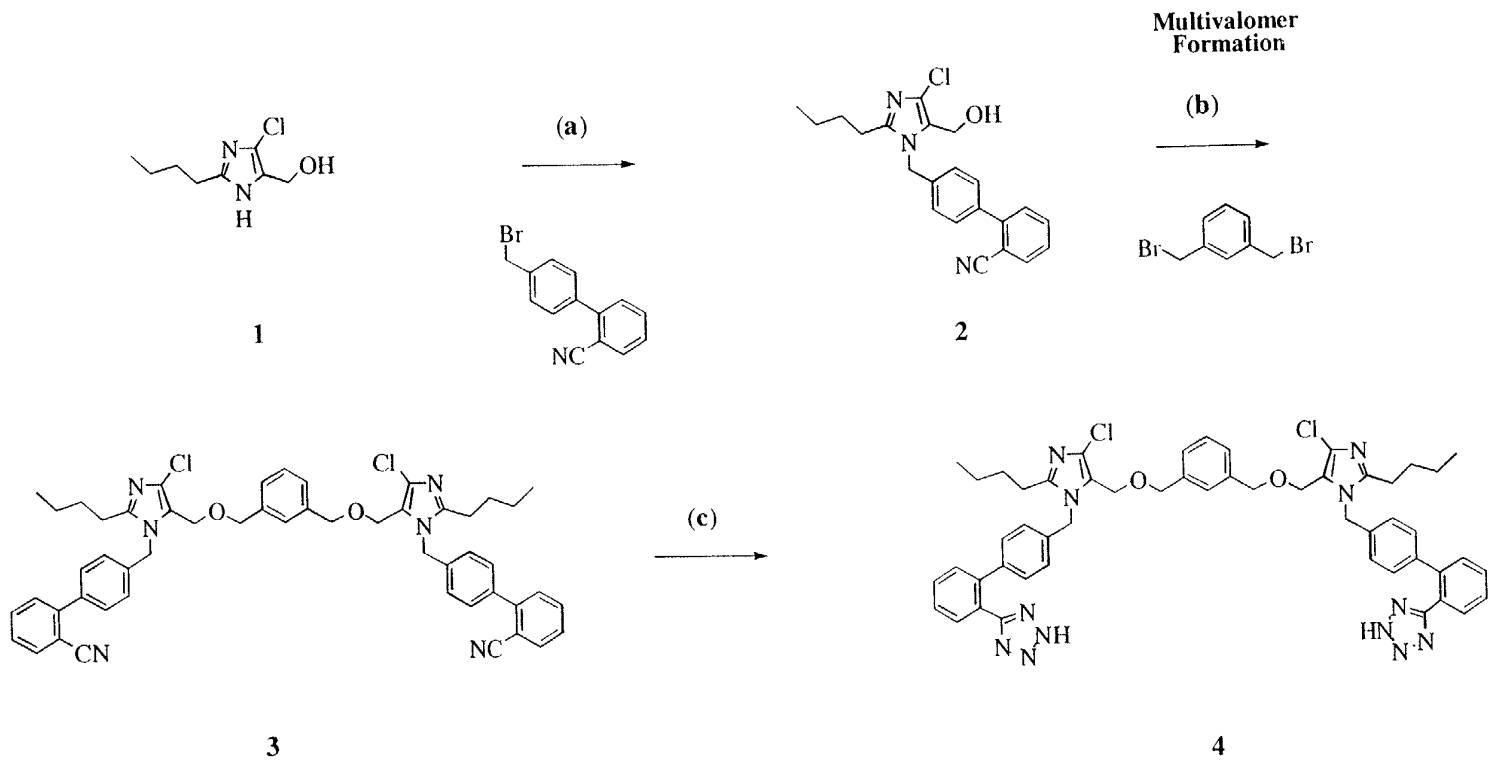
Losartan Multivalomer Synthesis 1-Hydroxyl Linked Multivalomer



(**a**) NaH, DMF (**b**) nBu_4NF, THF (**c**) NaH, DMF, $BrCH_2C_6H_4CH_2Br$ (**d**) HCl, MeOH.

FIGURE 44

Losartan Multivalomer Synthesis 2-Hydroxyl Linked Multivalomer



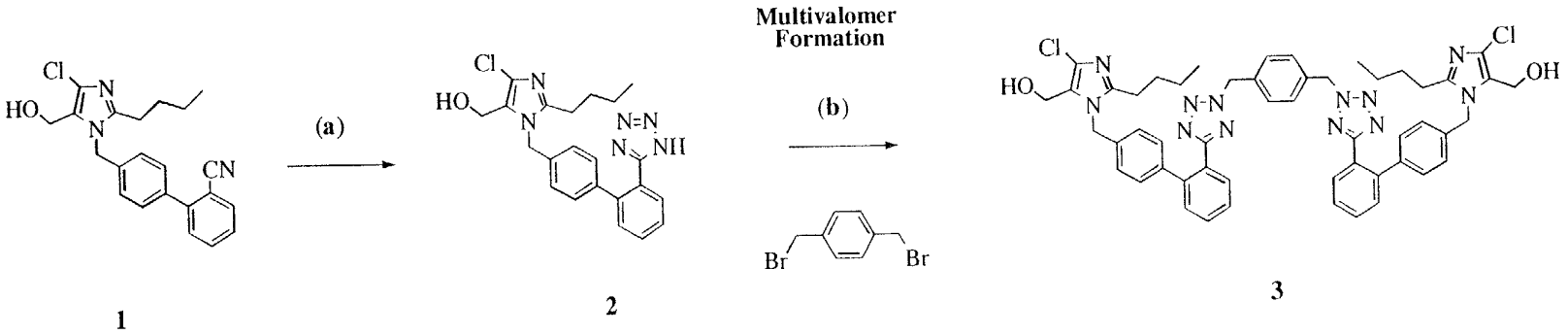
(a) NaOMe, MeOH, DMF **(b)** NaH, DMF **(c)** Bu_3SnN_3, xylene, reflux

FIGURE 45

TOETZT"hESSTOOT

Losartan Multivalomer Synthesis 3-Tetrazole Linked Multivalomers

Strategy-Sslective tetrazole alkylation in the presence of the primary hydroxyl



1 2 3

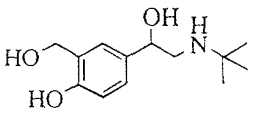
(a) Bu_3SnN_3, xylene, $_{24}$hr reflux (b) NaOH, THF

For precedent see Carini, D. J., *J. Med. Chem.*, **1991**, 34, 2525-2547

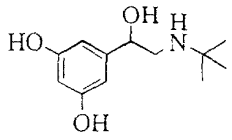
FIGURE 46

β_2 Adrenergic Drugs

1. Rapid Onset Inhaled Drugs

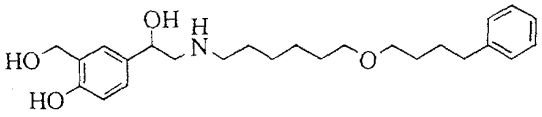


Albuterol
(GlaxoWellcome)

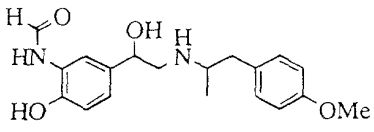


Terbutaline

2. Prolonged Duration of Action Inhaled Drugs



Salmeterol
(GlaxoWellcome)



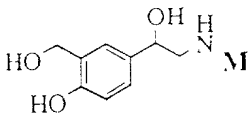
Formoterol
(Novartis)

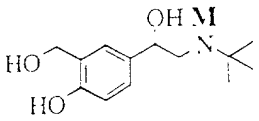
Notes-1. These drugs are racemates.Multivalomers will produce diastereomers.

FIGURE 47

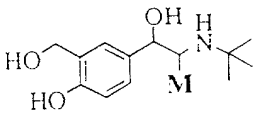
Albuterol Multivalomers

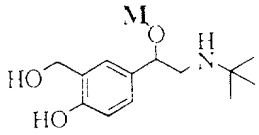
1. N atom





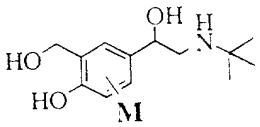
2. Ethanolamine function



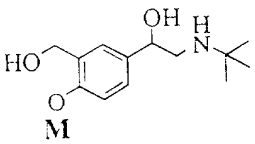


3. Phenyl Ring

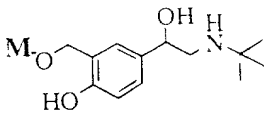
New Substitution



Phenolic Group



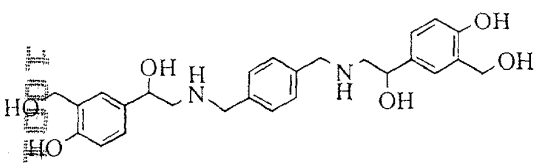
Benzyl Alcohol



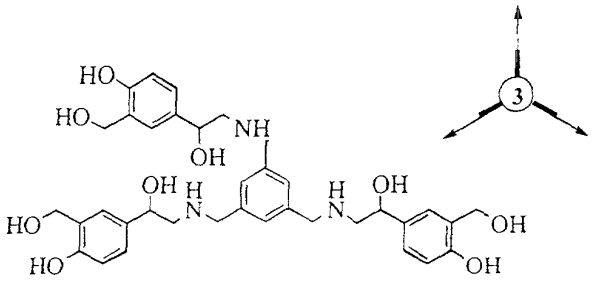
M represents a site for the attachment of the monovalomer to the framework core

FIGURE 48

1. Valency of Framework Building Block

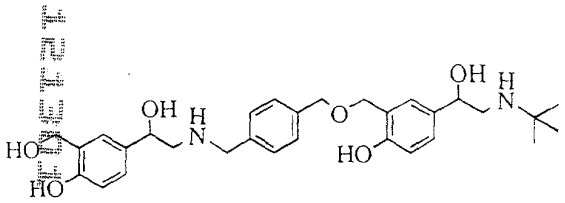


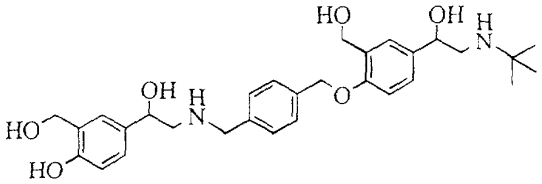
Dimeric Ligand



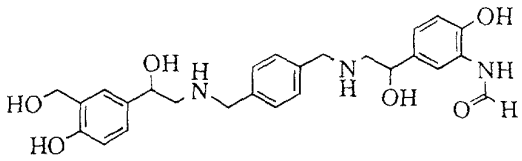
Trimeric Ligands

2. Relative Orientation of Monovalomer Building Blocks.

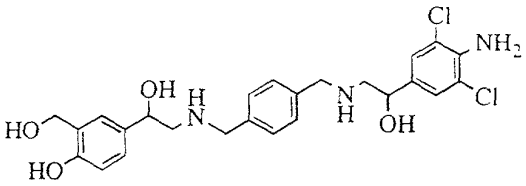




3. Mixed Multivalomers Derived from Different β_2-agonists



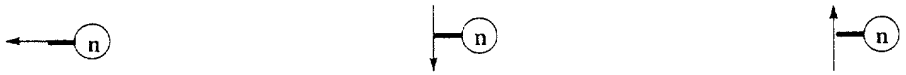
Albuterol/Formeterol



Albuterol/Clenbuterol

FIGURE 49

Albuterol Multivalomers 1-Different Points of Attachment



n defines the valency of the multivalomer

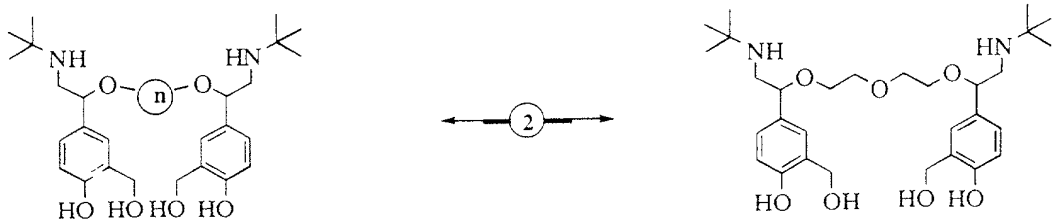
◯ defines the framework core

⟶ distinguishes the diff. ring points of attachment of albuterol

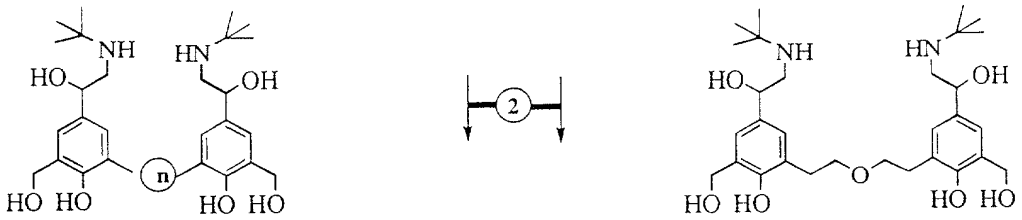
Generic Examples

SpecificExample

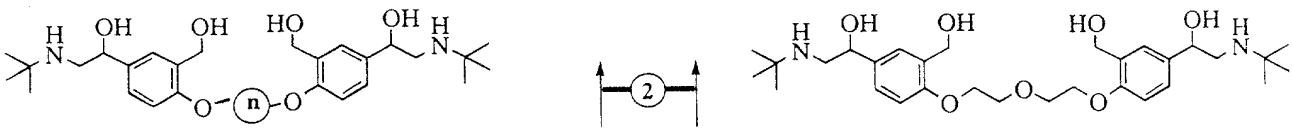
Series 1



Series 2



Series 3



Series 4

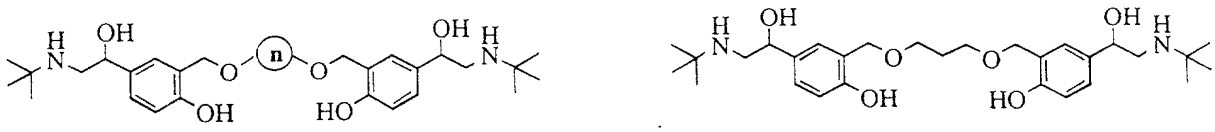
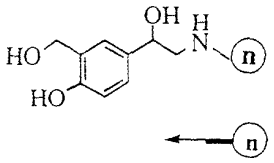


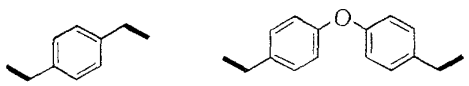
FIGURE 50

Albuterol Multivalomers 2-Alternative Framework Cores

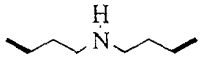


1. Alkyl Series

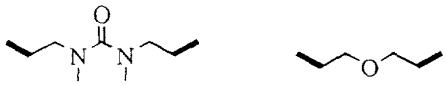
2. Aromatic Series



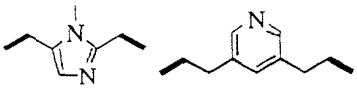
3. H-bond donor



4. H bond acceptor



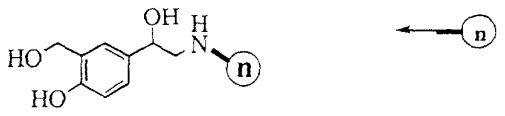
5. Basic

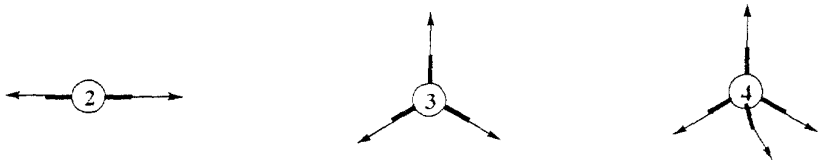


6. Acidic

FIGURE 51

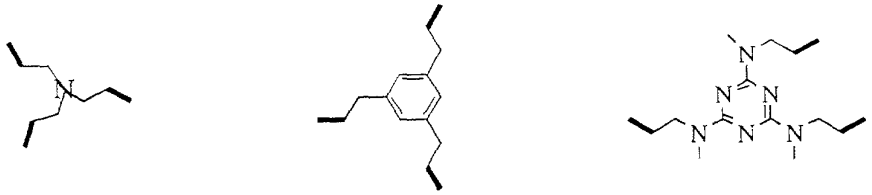
Albuterol Multivalomers 3-Alternative Framework Valency





Dimeric Series

Trimeric Series



Tetrameric Series

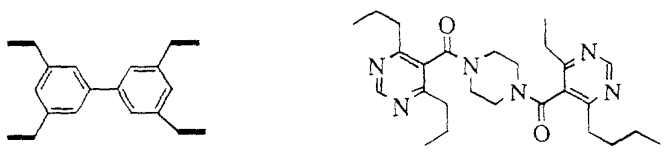


FIGURE 52

Albuterol Multivalomers 4-Relative Pharmacophore Orientation

Pharmacophore Orientation

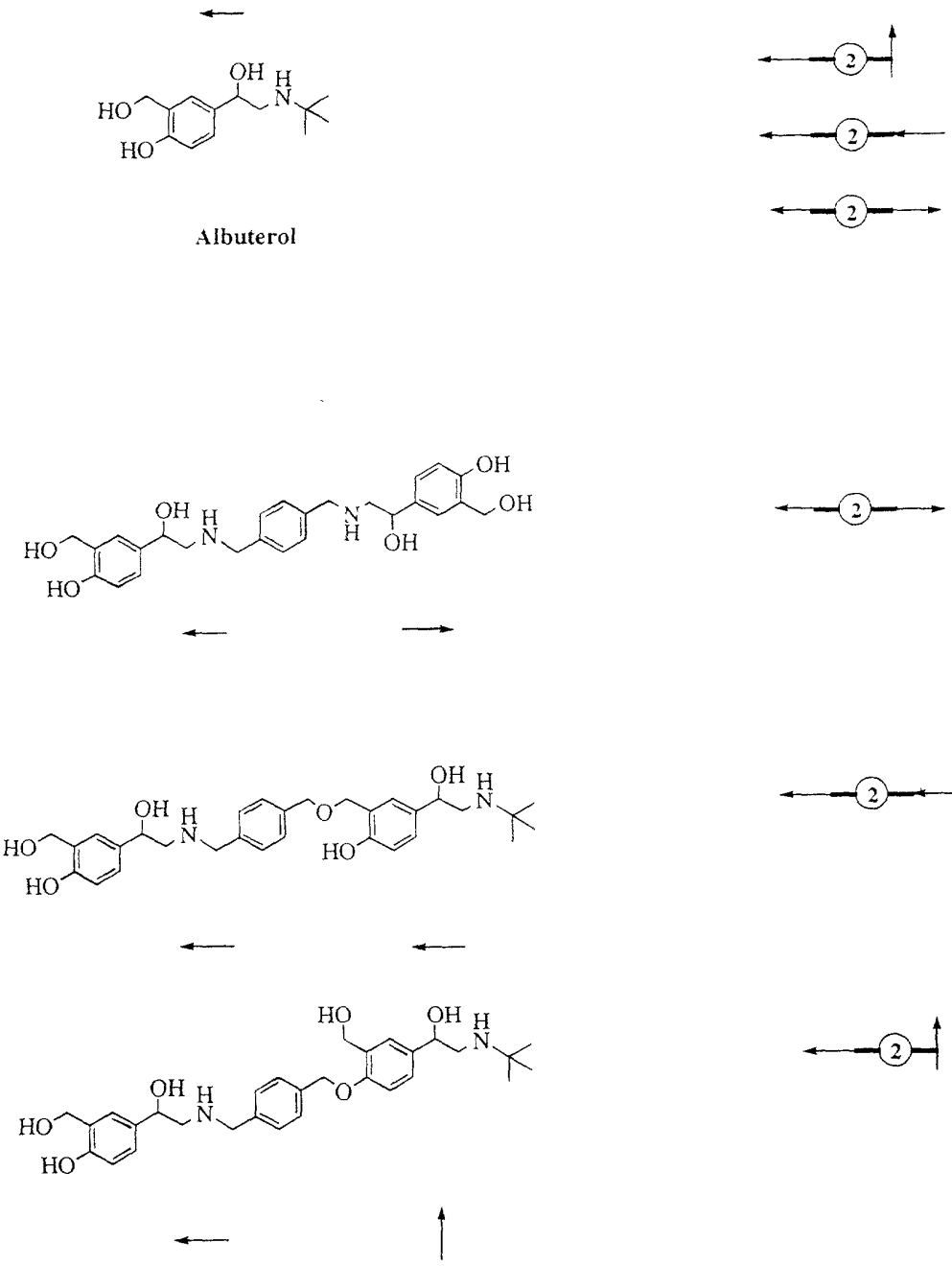
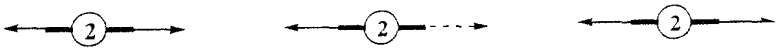
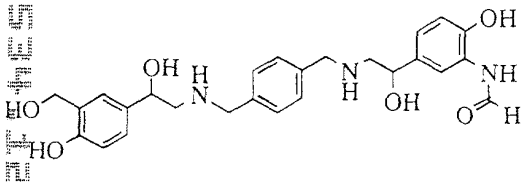


FIGURE 53

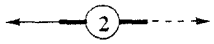
Albuterol Multivalomers 5-Mixed β_2 Adrenergic Heterovalomers

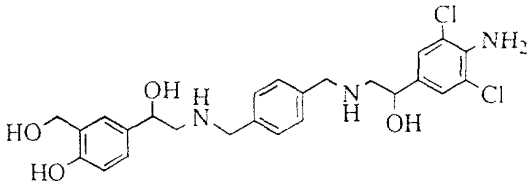
Heterovalomers





Albuterol/Formeterol





Albuterol/Clenbuterol

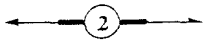
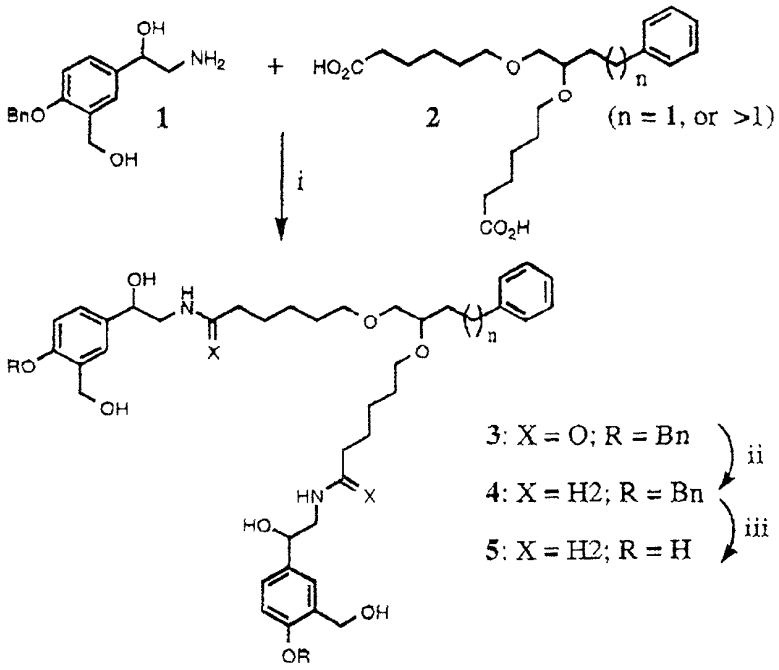
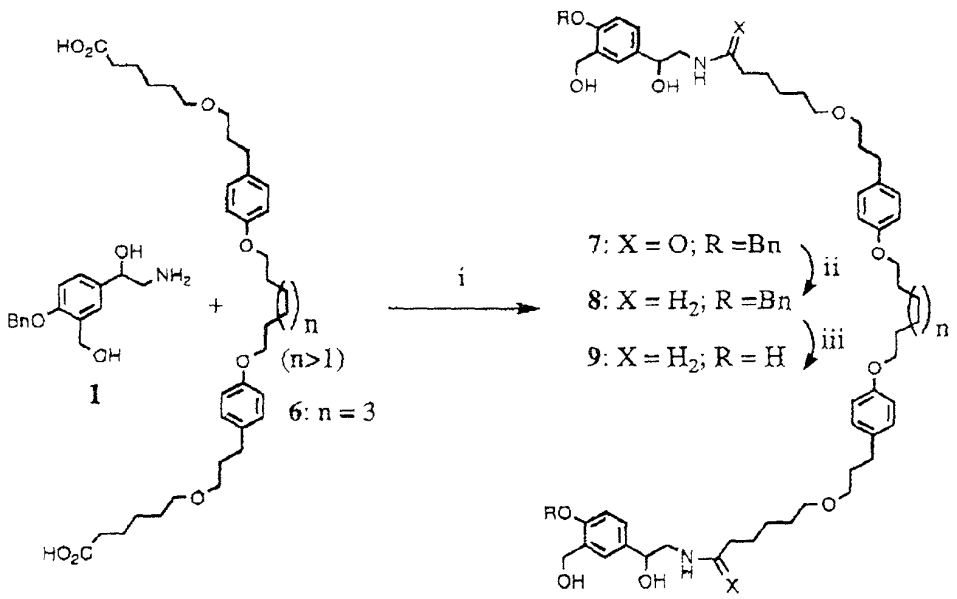


FIGURE 54



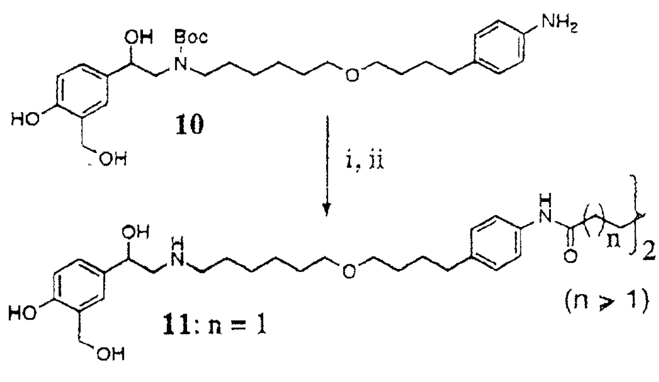
reagents and conditions: i) HOBt, PyBOP, DIPEA, DMF, rt, 24 h;
ii) $LiAlH_4$, THF, 0°C to 80°C; iii) H_2 (1 atm), 10% Pd/C, EtOH, rt, 24 h

FIGURE 55



reagents and conditions: i) HOBt. PyBOP, DIPEA, DMF, rt, 24 h;
ii) $LiAlH_4$, THF, 0°C to 80°C; iii) H_2 (1 atm), 10% Pd/C, EtOH, rt, 24 h

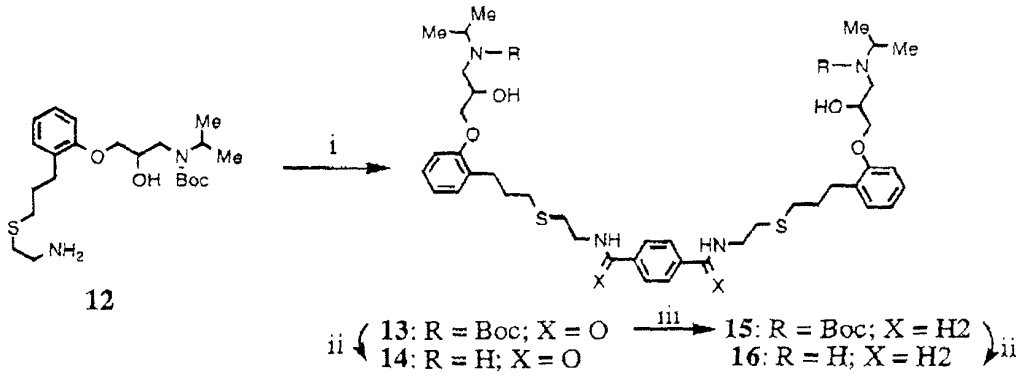
FIGURE 56



reagents and conditions: i) 1,6-hexanedioic acid, DIPEA, HOBT, PyBOP, DMF, rt; ii) TFA/CH_2Cl_2, 0°C

FIGURE 57

PCT/US94/05504



reagents and conditions: i) terphathalic acid, DIPEA, HOBT, PyBOP, DMF, rt: ii) TFA/CH_2Cl_2, 0°C; iii) $LiAlH_4$, THF, 80°C

FIGURE 58